

NEW USES FOR AMINO ACID ANTICONVULSANTS

RELATED APPLICATION

5 The present application is claiming benefit of
U.S. Serial Number 60/228,230 filed on August 25, 2000.

FIELD OF THE INVENTION

10 The present invention is directed to the novel
uses of a peptide class of compounds for treating bipolar
disorders and headaches, such as migraines and pain,
especially neuropathic pain.

BACKGROUND OF THE INVENTION

Bipolar disorders and headaches, such as
migraines, and pain, including neuropathic pain, are
varied maladies that on its face, are diverse.

15 A migraine headache is defined as a
periodically occurring vascular headache characterized by
pain in the head (usually unilateral), nausea, and
vomiting, photophobia, phonophobia, vertigo and general
weakness. Migraine is the most common type of vascular
20 headache and affects as many as 15% of the world's
population. Of the different types of migraines,
classical migraine and common migraine are the two most
prevalent. The major difference between the two types of
migraines is that classical migraines are preceded by the
25 appearance of neurological symptoms before an attack
whereas common migraines are not preceded by such
symptoms. Migraine is caused by intermittent brain
dysfunction. However, the precise pathophysiological
mechanisms involved are not understood. The head-pain is

believed to involve blood vessel dilation and a reduction in the brain's pain relieving chemicals.

Neuropathic pain, on the other hand, can be described as pain associated with damage or permanent alteration of the central nervous system. Clinical manifestations of neuropathic pain include a sensation of burning or electric shock, feelings of bodily distortion, allodynia and hyperalgesia.

It results from injury to a nerve. In contrast to the immediate pain caused by tissue injury, neuropathic pain can develop days or months after a traumatic injury. Furthermore, while pain caused by tissue injury is usually limited in duration to the period of tissue repair, neuropathic pain frequently is long lasting or chronic.

Moreover, neuropathic pain can occur spontaneously or as a result of stimulation that normally is not painful.

The clinical causes of neuropathic pain are widespread and include both trauma and disease. For example, traumatic nerve compression, or crush, and traumatic injury to the brain or spinal cord are common causes of neuropathic pain. Furthermore, most traumatic nerve injuries also cause the formation of neuromas, in which pain occurs as a result of aberrant nerve regeneration. In addition, cancer-related neuropathic pain is caused when tumor growth painfully compresses adjacent nerves, the brain or the spinal cord. Neuropathic pain is associated with diseases such as diabetes or alcoholism.

Bipolar disorder is a neuropsychiatric disorder. Also known as bipolar affective disorder (BAD) or manic-depressive illness, it is characterized by episodes of elevated mood (mania) and depression. The most severe and clinically distinctive forms of BAD are BP-I (severe bipolar affective (mood) disorder), which affects 2-3 million people in the U.S. and SAD-M (schizoaffective disorder manic type). They are characterized by at least one full episode of mania, with or without episodes of major depression (defined by lower mood or depression, with associated disturbances in rhythmic behaviors, such as sleeping, eating and sexual activity).

The therapies are varied. Analgesics are often used to treat infrequent and mild migraines. Analgesics reduce the pain of a migraine and in the case of aspirin also discourage clumping of blood platelets. However, for moderate to severe migraines, stronger medication is necessary, e.g., ergotamine or 5-H-T₁ agonists, like sumatriptan.

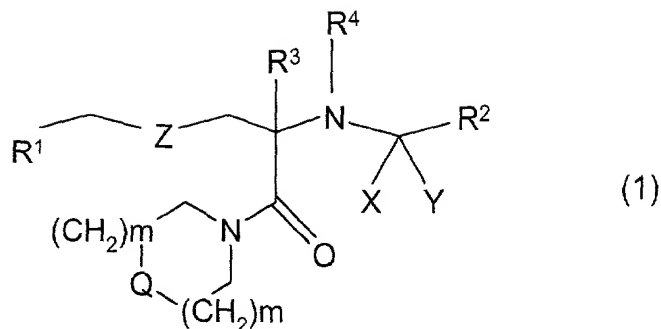
On the other hand, for neuropathic pain, opioid compounds (opiates) such as morphine may be utilized to treat the malady. Although effective as an analgesic, it is not always effective in treating neuropathic pain and may induce tolerance in patients. When a subject is tolerant to opioid narcotics, increased doses are required to achieve a satisfactory analgesic effect. At high doses, these compounds produce side effects, such as respiratory depression, which can be life threatening. In addition, opioids frequently produce physical

dependence in patients, which may be related to the dose of opioid taken and the period of time over which it is taken by the subject.

But neuropathic pain and bipolar disorder frequently are resistant to available drug therapies. In addition, current therapies have serious side-effects including, for example, cognitive changes, sedation, nausea, and in the case of narcotic drugs addictions. Many patients suffering from neuropathic pain are elderly or have other medical conditions that particularly limit their tolerance of the side-effects associated with available drug therapy.

The inadequacy of current therapy in relieving neuropathic pain and bipolar disorders without producing intolerable side-effects frequently is manifested in the depression and suicidal tendency of chronic pain sufferers. Moreover, the present drugs are not effective for completely alleviating the pain from those who have moderate to heavy migraine headaches.

U.S. Patent No. 5,885,999 discloses compounds which are useful for treating various maladies such as pain and headaches including migraines. These compounds are serine derivatives of the formula:



10 wherein m is zero, 1 or 2; and n is zero or 1, with the proviso that the sum total of m+n is 1 or 2;

R^1 represents phenyl; naphthyl; benzohydryl; or benzyl, where the naphthyl group or any phenyl moiety may be substituted;

15 R^2 represents hydrogen; phenyl; heteroaryl selected from indazolyl, thienyl, furanyl, pyridyl, thiazolyl, tetrazolyl and quinolinyl; naphthyl; benzohydryl; or benzyl; wherein each heteroaryl, naphthyl group and any phenyl moiety may be substituted;

20 R^3 and R^4 each independently represents hydrogen or C_{1-6} alkyl or R^3 and R^4 together are linked so as to form a C_{1-3} alkylene chain;

Q represents CR^5R^6 or NR^5 ;

25 X and Y each independently represents hydrogen, or together form a group =O; and

Z represents a bond O, S, SO, SO_2 , NR^c or $-(CR^cR^d)-m$ where R^c and R^d each independently represent hydrogen or C_{1-6} alkyl;

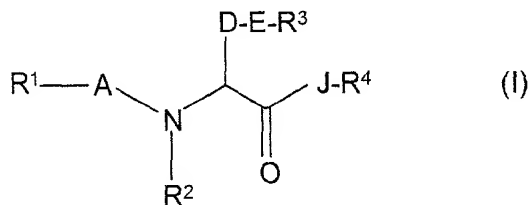
or a pharmaceutically acceptable salt thereof.

The compounds are alleged to be also useful in the treatment or prevention of inflammation, emesis and posttherapeutic neuralgia.

In U.S. Patent No. 6,228,825 to Tsai, et al.,
5 other amino acids and derivatives thereof are alleged to be useful for treating neuropsychiatric disorders, such as schizophrenia, Alzheimer's Disease, depression, autism, closed head injury, benign forgetfulness, childhood learning disorders, and attention deficit
10 disorders. These drugs include (i) D-alanine or modified form thereof, provided that the composition is substantially free of D-cycloserine and/or (ii) serine (or a modified form thereof), and/or (iii) 105 to 500 mg of D-cycloserine (or a modified form thereof); and/or
15 (iv) N-methylglycine (or a modified form thereof).

D-cycloserine, D-serine esters, D-serine or salts thereof have been disclosed to be useful in treating spinocerebellar degeneration. See, EP Application No. 1,084,704.

20 Peptides have also been alleged to be useful for treatment of pain and neurosis. More specifically, EPO application 997,147 discloses compounds of the formula:



30

wherein R¹ is

- 1) C1-15 alkyl,
- 2) C1-8 alkoxy,
- 3) phenyl,
- 5 4) C3-8 cycloalkyl,
- 5) hetero ring,
- 6) C1-4 alkyl substituted by phenyl, C3-8
cycloalkyl, or hetero ring,
- 7) C1-4 alkoxy substituted by phenyl, C3-8
10 cycloalkyl, or hetero ring, or
- 8) C2-4 alkenyl substituted by phenyl, C3-8
cycloalkyl, or hetero ring (with proviso that, all
phenyl, C3-8 cycloalkyl and hetero ring in R¹ group may
be substituted by 1-3 substituent selected from the
15 following (i)-(xi):
- (i) C1-4 alkyl,
- (ii) C1-4 alkoxy,
- (iii) phenyl,
- 20 (iv) phenoxy,
- (v) benzyloxy,
- (vi) -SR⁵ (in which R⁵ is hydrogen or C1-4
alkyl),
- (vii) C2-5 acyl,
- 25 (viii) halogen,
- (ix) C1-4 alkoxycarbonyl,
- (x) nitro,
- (xi) -NR⁶R⁷ (in which R⁶ and R⁷ each
independently, is hydrogen, C1-4 alkyl or C1-4
30 alkoxycarbonyl, or R⁶ and R⁷ taken together with the

nitrogen atom to which they are attached may represent 5-7 membered saturated hetero ring containing another one nitrogen atom or one oxygen atom));

A is a bond, -CO- or -SO₂-;

5 R² is hydrogen or C1-4 alkyl optionally substituted by one phenyl;

D is C1-4 alkylene or C2-4 alkenylene;

E is

- 10 1) -COO-,
 2) -OCO-,
 3) -CONR⁸ (in which R⁸ is hydrogen or C1-4 alkyl),
 4) -NR⁹CO- (in which R⁹ is hydrogen or C1-4 alkyl),
15 5) -O-,
 6) -S-,
 7) -SO-,
 8) -SO₂-,
 9) -NR¹⁰- (in which R¹⁰ is hydrogen or C1-4
20 alkyl),
 10) -CO-,
 11) -SO₂NR¹¹- (in which R¹¹ is hydrogen or C1-4 alkyl) or
 12) -NR¹²SO₂- (in which R¹² is hydrogen or
25 C1-4 alkyl);

R³ is

- 1) carbocyclic ring,
- 2) hetero ring, or

3) C1-4 alkyl substituted by carbocyclic ring or hetero ring (with proviso that, all carbocyclic ring and hetero ring in R^3 may be substituted by 1-3 substituents selected from the following (i)-(xi);

- 5 (i) C1-4 alkyl,
(ii) C1-4 alkoxy,
(iii) phenyl,
(iv) phenoxy,
(v) benzyloxy,
10 (vi) $-SR^{13}$ (in which R^{13} is hydrogen or C1-4 alkyl),
(vii) C2-5 acyl,
(viii) halogen,
(ix) C1-4 alkoxy carbonyl,
15 (x) nitro,
(xi) $-NR^{14}R^{15}$ (in which R^{14} and R^{15} , each independently, is hydrogen, C1-4 alkyl or C1-4 alkoxy carbonyl, or R^{14} and R^{15} taken together with the
20 nitrogen atom to which they are attached may represent 5-7 membered saturated hetero ring containing another one nitrogen atom or one oxygen atom);

J is $-O-$ or $-NR^{16}-$ (in which R^{16} is hydrogen or C1-4 alkyl);

25 R^4 is

- 1) C1-8 alkyl,
2) carbocyclic ring,
3) hetero ring,
4) C1-8 alkyl substituted by 1-3 of substituent
30 selected from the following (i)-(v);

- (i) carbocyclic ring,
(ii) hetero ring,
(iii) COOR¹⁷ (in which R¹⁷ is hydrogen or
C1-4 alkyl substituted by one phenyl (in which phenyl may
be substituted by C1-4 alkoxy),
(iv) SR¹⁸ (in which R¹⁸ is hydrogen or C1-4
alkyl),
(v) OR¹⁹ (in which R¹⁹ is hydrogen or C14
alkyl), or

when J represents -NR¹⁶- group, R⁴ and R¹⁶ taken together
with the nitrogen atom to which they are attached may
represent hetero ring (with proviso that, all carbocyclic
ring and hetero ring, and hetero ring represented by R⁴
and R¹⁶ taken together with the nitrogen atom to which
they are attached may be substituted by 1-3 of
substituent selected from the following (i)-(xi);

- (i) C1-4 alkyl,
(ii) C1-4 alkoxy,
(iii) phenyl,
(iv) phenoxy,
(v) benzyloxy,
(vi) -SR²⁰ (in which R²⁰ is hydrogen or C1-4
alkyl),
(vii) C2-5 acyl,
(viii) halogen,
(ix) C1-4 alkoxycarbonyl,
(x) nitro,
(xi) -NR²¹R²² (in which R²¹ and R²² each
independently, is hydrogen, C1-4 alkyl or C1-4

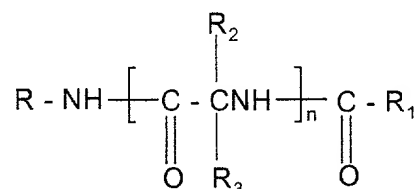
alkoxycarbonyl, or R²¹ and R²² taken together with the nitrogen atom to which they are attached may represent 5-7 membered saturated hetero ring containing another one nitrogen atom or one oxygen atom),

5

non-toxic salt thereof, or a hydrate thereof.

Other peptides are known to exhibit central nervous system (CNS) activity and are useful in the treatment of epilepsy and other CNS disorders. These peptides, which are described in U.S. Patent No. 5,378,729, to Kohn, et al., have the formula:

15



wherein

20

R is hydrogen, lower alkyl, lower alkenyl, lower alkynyl, aryl, aryl lower alkyl, heterocyclic, heterocyclic lower alkyl, lower alkyl heterocyclic, lower cycloalkyl, lower cycloalkyl lower alkyl, and R is unsubstituted or is substituted with at least one electron withdrawing group or electron donating group;

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R₁ is hydrogen or lower alkyl, lower alkenyl, lower alkynyl, aryl lower alkyl, aryl, heterocyclic lower alkyl, heterocyclic, lower cycloalkyl, lower cycloalkyl lower alkyl, each unsubstituted or substituted with an

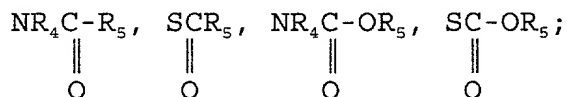
electron donating group or an electron withdrawing group;
and

R_2 and R_3 are independently hydrogen, lower alkyl, lower alkenyl, lower alkynyl, aryl lower alkyl, aryl, heterocyclic, heterocyclic lower alkyl, lower alkyl heterocyclic, lower cycloalkyl, lower cycloalkyl lower alkyl, or Z-Y wherein R_2 and R_3 may be unsubstituted or substituted with at least one electron withdrawing group or electron donating group;

Z is O, S, $S(O)_a$, NR_4 , PR_4 or a chemical bond;

Y is hydrogen, lower alkyl, aryl, aryl lower alkyl, lower alkenyl, lower alkynyl, halo, heterocyclic, heterocyclic lower alkyl, and Y may be unsubstituted or substituted with an electron donating group or an electron withdrawing group, provided that when Y is halo, Z is a chemical bond, or

ZY taken together is $NR_4NR_5R_7$, NR_4OR_5 , ONR_4R_7 , OPR_4R_5 , PR_4OR_5 , SNR_4R_7 , NR_4SR_7 , SPR_4R_5 or PR_4SR_7 , $NR_4PR_5R_6$ or $PR_4NR_5R_7$,



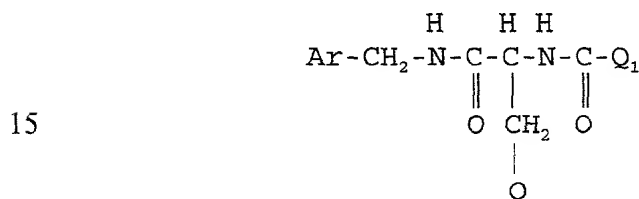
R_4 , R_5 and R_6 are independently hydrogen, lower alkyl, aryl, aryl lower alkyl, lower alkenyl, or lower alkynyl, wherein R_4 , R_5 and R_6 may be unsubstituted or substituted with an electron withdrawing group or an electron donating group; and

R_7 is R_6 or $COOR_8$ or COR_8 ;

R₈ is hydrogen or lower alkyl, or aryl lower alkyl, and the aryl or alkyl group may be unsubstituted or substituted with an electron withdrawing group or an electron donating group; and

5 n is 1-4; and
 a is 1-3.

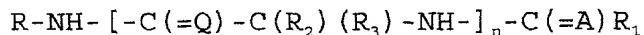
U.S. Patent No. 5,773,475, the contents of which are incorporated by reference, also discloses additional compounds useful for treating CNS disorders.
10 These compounds are N-benzyl-2-amino-3-methoxypropionamides having the formula:



wherein

Ar is aryl which is unsubstituted or
20 substituted with halo;
 Q is lower alkoxy; and
 Q₁ is CH₃.

Harris in U.S. Patent No. 6,133,261 describes a method of treating or preventing stroke in a human by
25 administering thereto an effective amount of a compound of the formula:



wherein

5 R is hydrogen, lower alkyl, lower alkenyl, lower alkynyl, aryl, aryl (lower alkyl), heterocyclic, heterocyclic (lower alkyl), (lower alkyl) heterocyclic, lower cycloalkyl, lower cycloalkyl (lower alkyl), and R

5 is unsubstituted or is substituted with at least one electron withdrawing group, or electron donating group;

R_1 is hydrogen or lower alkyl, lower alkenyl, lower alkynyl, aryl (lower alkyl), aryl, heterocyclic, (lower alkyl) heterocyclic, heterocyclic (lower alkyl),
10 lower cycloalkyl, lower cycloalkyl (lower alkyl), each unsubstituted or substituted with an electron donating group or an electron withdrawing group and

R_2 and R_3 are independently hydrogen, lower alkyl, lower alkenyl, lower alkynyl, aryl (lower alkyl),
15 aryl, heterocyclic, heterocyclic (lower alkyl), (lower alkyl) heterocyclic, lower cycloalkyl, lower cycloalkyl (lower alkyl), SO_3^- , or Z-Y where R_2 and R_3 may be unsubstituted or substituted with at least one electron withdrawing group or electron donating group;

20 Z is O, S, $S(O)_a$, NR_4 , PR_4 or a chemical bond;

Y is hydrogen, lower alkyl, aryl, aryl(lower alkyl), lower alkenyl, lower alkynyl, halo, heterocyclic, heterocyclic (lower alkyl), (lower alkyl)heterocyclic, cycloalkyl, cycloalkyl (lower alkyl) and Y may be
25 unsubstituted or substituted with an electron donating group or an electron withdrawing group, provided that when Y is halo, Z is a chemical bond;

or ZY taken together is $NR_4NR_5R_7$, NR_4OR_5 , ONR_4R_7 , OPR_4R_5 , PR_4OR_5 , SNR_4R_7 , NR_4SR_7 , SPR_4R_5 , PR_4SR_7 , $NR_4PR_5R_6$,
30 $PR_4NR_5R_7$, $NR_4C(O)R_5$, $SC(O)R_5$, $NR_4CO_2R_5$, SCO_2R_5 , $NR_4C(O)R_5R_6$, $NR_4C(O)NR_5S(O)_aR_6$, $NR_4C(S)R_5R_6$, $NR_4C(=Q)MNR_5C(=A)OR_6$, or $C(S)NH_2$;

R_4 , R_5 and R_6 are independently hydrogen, lower alkyl, aryl, aryl (lower alkyl), lower alkenyl, or lower

5 alkynyl, wherein R_4 , R_5 and R_6 may be unsubstituted or substituted with an electron withdrawing group or an electron donating group;

R_7 is R_6 , $COOR_8$, or $C(O)R_8$;

10 R_8 is hydrogen or lower alkyl, or aryl (lower alkyl), and the aryl or alkyl group may be unsubstituted or substituted with an electron withdrawing group or an electron donating group;

A and Q are independently O or S;

15 M is an alkylene chain containing up to 6 carbon atoms or a chemical bond;

n is 1-4; and

a is 1-3;

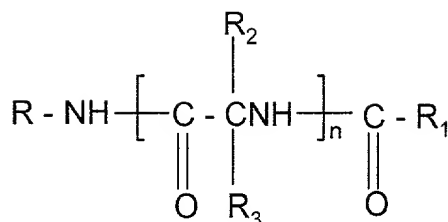
or a pharmaceutically acceptable salt thereof.

20 The present inventor has found that these peptides in U.S. Patent No. 5,378,729 and 5,773,475, are useful for treating pain, including neuropathic pain, and headaches, including migraines and bipolar disorders. Moreover, these compounds are not addictive and do not exhibit the side effects of the commercially available
25 drugs described hereinabove.

SUMMARY OF THE INVENTION

Accordingly, the present invention is directed to the method of treating bipolar disease in a patient suffering from same which comprises administering thereto
30 an amount effective to treat such bipolar disease of a compound having Formula I:

5



10

I

wherein

15 R is hydrogen, lower alkyl, lower alkenyl, lower alkynyl, aryl, aryl lower alkyl, heterocyclic, heterocyclic lower alkyl, lower alkyl heterocyclic, lower cycloalkyl, lower cycloalkyl lower alkyl, and R is unsubstituted or is substituted with at least one electron withdrawing group, or electron donating group;

20 R₁ is hydrogen or lower alkyl, lower alkenyl, lower alkynyl, aryl lower alkyl, aryl, heterocyclic lower alkyl, heterocyclic, lower alkyl heterocyclic, lower cycloalkyl, lower cycloalkyl lower alkyl, each unsubstituted or substituted with an electron donating group or an electron withdrawing group; and

25 R₂ and R₃ are independently hydrogen, lower alkyl, lower alkenyl, lower alkynyl, aryl lower alkyl, aryl, heterocyclic, heterocyclic lower alkyl, lower alkyl heterocyclic, lower cycloalkyl, lower cycloalkyl lower alkyl, halo or Z-Y wherein R₂ and R₃ may be unsubstituted or substituted with at least one electron withdrawing group or electron donating group;

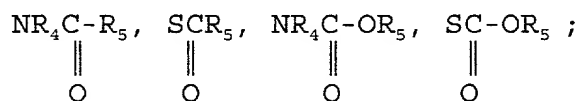
30

Z is O, S, S(O)_a, NR₄, or PR₄;

Y is hydrogen, lower alkyl, aryl, aryl lower alkyl, lower alkenyl, lower alkynyl, halo, heterocyclic,

5 heterocyclic lower alkyl, lower alkyl heterocyclic, lower
cycloalkyl, lower cycloalkyl lower alkyl, and Y may be
unsubstituted or substituted with an electron donating
group or an electron withdrawing group, or

10 ZY taken together is $\text{NR}_4\text{NR}_5\text{R}_7$, NR_4OR_5 , ONR_4R_7 ,
 OPR_4R_5 , PR_4OR_5 , SNR_4R_7 , NR_4SR_7 , SPR_4R_5 or PR_4SR_7 , $\text{NR}_4\text{PR}_5\text{R}_6$ or
 $\text{PR}_4\text{NR}_5\text{R}_7$,



20 R_4 , R_5 and R_6 are independently hydrogen, lower
alkyl, aryl, aryl lower alkyl, lower alkenyl, or lower
alkynyl, wherein R_4 , R_5 and R_6 may be unsubstituted or
substituted with an electron withdrawing group or an
electron donating group;

R_7 is independently R_6 or COOR_8 or COR_8 ;

25 R_8 is hydrogen or lower alkyl, or aryl lower
alkyl, and the aryl or alkyl group may be unsubstituted
or substituted with an electron withdrawing group or an
electron donating group; and

n is 1-4; and

a is 1-3.

30 The present invention is also directed to the
method of treating pain in a patient suffering from same
which comprises administering to said patient a pain
alleviating effective amount of said compound to treat
the pain.

35 In another aspect, the present invention is
directed to a method of treating headaches, including

5 migraine headaches, in a patient suffering from same
which comprises administering to said patient a headache
alleviating effective amount of said compound.

DETAILED DESCRIPTION OF THE INVENTION

10 As indicated hereinabove, the compounds of
Formula I are useful for treating pain, including
neuropathic pain and headaches, including migraine
headaches, and bipolar disorders. These compounds are
described in U.S. Patent No. 5,378,729, the contents of
15 which are incorporated by reference.

 As defined herein, the "alkyl" groups when used
alone or in combination with other groups, are lower
alkyl containing from 1 to 6 carbon atoms and may be
straight chain or branched. These groups include methyl,
20 ethyl, propyl, isopropyl, butyl, isobutyl, tertiary
butyl, amyl, hexyl, and the like.

 The "aryl lower alkyl" groups include, for
example, benzyl, phenethyl, phenpropyl, phenisopropyl,
phenbutyl, diphenylmethyl, 1,1-diphenylethyl, 1,2-
25 diphenylethyl, and the like.

 The term "aryl", when used alone or in
combination, refers to an aromatic group which contains
from 6 up to 18 ring carbon atoms and up to a total of 25
carbon atoms and includes the polynuclear aromatics.
30 These aryl groups may be monocyclic, bicyclic, tricyclic
or polycyclic and are fused rings. A polynuclear
aromatic compound, as used herein, is meant to encompass
bicyclic and tricyclic fused aromatic ring systems
containing from 10-18 ring carbon atoms and up to a total

5 of 25 carbon atoms. The aryl group includes phenyl, and the polynuclear aromatics e.g., naphthyl, anthracenyl, phenanthrenyl, azulenyl and the like. The aryl group also includes groups like ferrocenyl.

10 "Lower alkenyl" is an alkenyl group containing from 2 to 6 carbon atoms and at least one double bond. These groups may be straight chained or branched and may be in the Z or E form. Such groups include vinyl, propenyl, 1-butenyl, isobutenyl, 2-butenyl, 1-pentenyl, (Z)-2-pentenyl, (E)-2-pentenyl, (Z)-4-methyl-2-pentenyl, (E)-4-methyl-2-pentenyl, pentadienyl, e.g., 1, 3- or 2,4-
15 pentadienyl, and the like.

The term "lower alkynyl" is an alkynyl group containing 2 to 6 carbon atoms and may be straight chained as well as branched. It includes such groups as
20 ethynyl, propynyl, 1-butyne, 2-butyne, 1-pentyne, 2-pentyne, 3-methyl-1-pentyne, 3-pentyne, 1-hexyne, 2-hexyne, 3-hexyne and the like.

The term "lower cycloalkyl" when used alone or in combination is a cycloalkyl group containing from 3 to
25 18 ring carbon atoms and up to a total of 25 carbon atoms. The cycloalkyl groups may be monocyclic, bicyclic, tricyclic, or polycyclic and the rings are fused. The cycloalkyl may be completely saturated or partially saturated. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl,
30 cyclooctyl, cyclodecyl, cyclohexenyl, cyclopentenyl, cyclooctenyl, cycloheptenyl, decalinyl, hydroindanyl, indanyl, fenchyl, pinenyl, adamantyl, and the like. Cycloalkyl includes the cis or trans forms. Furthermore,

5 the substituents may either be in endo or exo positions
in the bridged bicyclic systems.

10 The term "electron-withdrawing and electron
donating" refer to the ability of a substituent to
withdraw or donate electrons, respectively, relative to
that of hydrogen if the hydrogen atom occupied the same
position in the molecule. These terms are well
understood by one skilled in the art and are discussed in
Advanced Organic Chemistry, by J. March, John Wiley and
Sons, New York, NY, pp. 16-18 (1985) and the discussion
therein is incorporated herein by reference. Electron
withdrawing groups include halo, including bromo, fluoro,
chloro, iodo and the like; nitro, carboxy, lower alkenyl,
lower alkynyl, formyl, carboxyamido, aryl, quaternary
ammonium, trifluoromethyl, aryl lower alkanoyl,
carbalkoxy and the like. Electron donating groups
include such groups as hydroxy, lower alkoxy, including
methoxy, ethoxy and the like; lower alkyl, such as
methyl, ethyl, and the like; amino, lower alkylamino,
di(loweralkyl) amino, aryloxy such as phenoxy; mercapto,
lower alkylthio, disulfide (lower alkyl dithio) and the
like. One of ordinary skill in the art will appreciate
that some of the aforesaid substituents may be considered
to be electron donating or electron withdrawing under
different chemical conditions. Moreover, the present
invention contemplates any combination of substituents
selected from the above-identified groups.

The term "halo" includes fluoro, chloro, bromo,
iodo and the like.

The term "acyl" includes lower alkanoyl.

5 As employed herein, the heterocyclic
substituent contains at least one sulfur, nitrogen or
oxygen ring atom, but also may include one or several of
said atoms in the ring, but preferably no more than 4
heteroatoms in the ring. The heterocyclic substituents
10 contemplated by the present invention include
heteroaromatics and saturated and partially saturated
heterocyclic compounds. These heterocyclics may be
monocyclic, bicyclic, tricyclic or polycyclic and are
fused rings. They may contain from 3 up to 18 ring atoms
15 and up to a total of 17 ring carbon atoms and a total of
up to 25 carbon atoms. The heterocyclics are also
intended to include the so-called benzoheterocyclics.
Representative heterocyclics include furyl, thienyl,
pyrazolyl, pyrrolyl, imidazolyl, indolyl, thiazolyl,
20 oxazolyl, isothiazolyl, isoxazolyl, piperidyl,
pyrrolinyl, piperazinyl, quinolyl, triazolyl, tetrazolyl,
isoquinolyl, benzofuryl, benzothienyl, morpholinyl,
benzoxazolyl, tetrahydrofuryl, pyranyl, indazolyl,
purinyl, indolinyl, pyrazolindinyl, imidazolinyl,
25 imadazolindinyl, pyrrolidinyl, furazanyl, N-
methylindolyl, methylfuryl, pyridazinyl, pyrimidinyl,
pyrazinyl, pyridyl, epoxy, aziridino, oxetanyl,
azetidiny, the N-oxides of the nitrogen containing
heterocycles, such as the nitric oxides of pyridyl,
30 pyrazinyl, and pyrimidinyl and the like. The preferred
heterocyclics are thienyl, furyl, pyrrolyl, benzofuryl,
benzothienyl, indolyl, methylpyrrolyl, morpholinyl,
pyridyl, pyrazinyl, imidazolyl, pyrimidinyl, and
pyridazinyl. The preferred heterocyclic is a 5 or 6-

5 membered heterocyclic compound. The especially preferred heterocyclic is furyl, pyridyl, pyrazinyl, imidazolyl, pyrimidinyl, and pyridazinyl. The most preferred heterocyclic is furyl, pyridyl, thiazolyl and thienyl.

10 The preferred compounds are those wherein n is 1, but di, tri and tetrapeptides are also contemplated to be within the scope of the claims.

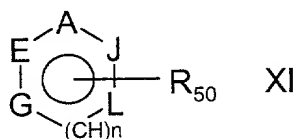
15 The preferred values of R is aryl lower alkyl, especially benzyl, especially those wherein the phenyl ring thereof is unsubstituted or substituted with electron donating groups or electron withdrawing groups, such as halo (e.g., F).

 The preferred R_1 is H or lower alkyl. The most preferred R_1 group is methyl.

20 The most preferred electron donating substituents and electron withdrawing substituents are halo, nitro, alkanoyl, formyl, arylalkanoyl, aryloyl, carboxyl, carbalkoxy, carboxamido, cyano, sulfonyl, sulfoxide, heterocyclic, guanidine, quaternary ammonium, lower alkenyl, lower alkynyl, sulfonium salts, hydroxy, 25 lower alkoxy, lower alkyl, amino, lower alkylamino, di(loweralkyl)amino, amino lower alkyl, mercapto, lower alkylthio, and lower alkylldithio. The term "sulfide" encompasses mercapto, and alkylthio, while the term disulfide encompasses alkylldithio. It is more preferred 30 that the electron donating groups and electron withdrawing groups do not contain a cyclic group. The electron donating and electron withdrawing groups may be substituted on any one of R_1 , R_2 , R_3 , R_4 , R_5 or R_6 , R_7 or R_8 as defined herein.

5 The ZY groups representative of R_2 and R_3
include hydroxy, alkoxy, such as methoxy, ethoxy,
aryloxy, such as phenoxy; thioalkoxy, such as
thiomethoxy, thioethoxy; thioaryloxy such as thiophenoxy;
amino; alkylamino, such as methylamino, ethylamino;
10 arylmino, such as anilino; lower dialkylamino, such as,
dimethylamino; trialkyl ammonium salt; hydrazino;
alkylhydrazino and arylhydrazino, such as N-
methylhydrazino, N-phenylhydrazino, carbalkoxy hydrazino,
aralkoxycarbonyl hydrazino, aryloxycarbonyl hydrazino,
15 hydroxylamino, such as N-hydroxylamino (-NH-OH), lower
alkoxy amino [(NHOR₁₈) wherein R₁₈ is lower alkyl], N-lower
alkylhydroxyl amino [(NR₁₈)OH wherein R₁₈ is lower alkyl],
N-lower alkyl-O-lower alkylhydroxyamino, i.e., [N(R₁₈)OR₁₉
wherein R₁₈ and R₁₉ are independently lower alkyl] and o-
20 hydroxylamino (-O-NH₂); alkylamido such as acetamido;
trifluoroacetamido; lower alkoxyamino, (e.g., NH(OCH₃);
and heterocyclicamino, such as pyrazoylamino.

 The preferred heterocyclic groups
representative of R_2 and R_3 are monocyclic heterocyclic
25 moieties of the formula:



30 or those corresponding partially or fully saturated form
thereof wherein n is 0 or 1; and

R_{50} is H or an electron withdrawing group or
electron donating group;

5 A, Z, L and J are independently CH, or a
heteroatom selected from the group consisting of N, O, S;
and

 G is CH, or a heteroatom selected from the
group consisting of N, O and S,

10 but when n is O, G is CH, or a heteroatom
selected from the group consisting of NH, O and S with
the proviso that at most two of A, E, L, J and G are
heteroatoms.

 When n is O, the above heteroaromatic moiety is
15 a five membered ring, while if n is 1, the heterocyclic
moiety is a six membered monocyclic heterocyclic moiety.
The preferred heterocyclic moieties are those
aforementioned heterocyclics which are monocyclic.

 Thus, the most preferred monocyclic
20 heterocyclic definition of R₂ and R₃ is furyl thienyl,
thiazolyl, and pyridyl.

 If the ring depicted hereinabove contains a
nitrogen ring atom, then the N-oxide forms are also
contemplated to be within the scope of the invention.

25 When R₂ or R₃ is a heterocyclic of the above
formula, it may be bonded to the main chain by a ring
carbon atom. When n is O, R₂ or R₃ may additionally be
bonded to the main chain by a nitrogen ring atom.

 Other preferred moieties of R₂ and R₃ are
30 hydrogen, aryl, e.g., phenyl, aryl alkyl, e.g., benzyl
and alkyl.

 It is to be understood that the preferred
groups of R₂ and R₃ may be unsubstituted or substituted
with electron donating or electron withdrawing groups.

5 It is preferred that the electron withdrawing group or electron donating group does not contain a cyclic group, unless the electron withdrawing group or electron donating group is a hydrocarbyl group that contains only carbon and hydrogen atoms.

10 It is more preferred that R_2 and R_3 are independently hydrogen, lower alkyl, which is either unsubstituted or substituted with an electron withdrawing group or an electron donating group, such as lower alkoxy (e.g., methoxy, ethoxy, and the like), N-hydroxylamino, 15 N-lower alkylhydroxyamino, N-loweralkyl-O-loweralkyl and alkylhydroxyamino.

It is even more preferred that one of R_2 and R_3 is hydrogen; while the other is one of the preferred group indicated hereinabove.

20 It is preferred that n is one.

It is preferred that R_2 is hydrogen and R_3 is hydrogen, an alkyl group which is unsubstituted or substituted by at least an electron donating or electron withdrawing group or ZY. In this preferred embodiment, 25 it is more preferred that R_3 is hydrogen or an alkyl group such as methyl, which is unsubstituted or substituted by an electron donating group, NR_4OR_5 or ONR_4R_7 , wherein R_4 , R_5 and R_7 are independently hydrogen or lower alkyl. It is preferred that the electron donating group is lower alkoxy, and especially methoxy or ethoxy. 30

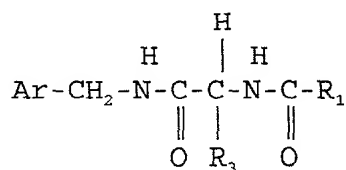
It is also preferred that R is aryl lower alkyl. The most preferred aryl for R is phenyl. The most preferred R group is benzyl. In a preferred embodiment, the aryl group may be unsubstituted or

5 substituted with an electron donating or electron
withdrawing group. If the aryl ring in R is substituted,
it is most preferred that it is substituted with an
electron withdrawing group, especially on the aryl ring.
The most preferred electron withdrawing group for R is
10 halo, especially fluoro.

The preferred R_1 is loweralkyl, especially
methyl.

The more preferred compounds are compounds of
formula I wherein n is 1; R_2 is hydrogen; R_3 is hydrogen,
15 an alkyl group, especially methyl which is substituted by
an electron donating or electron withdrawing group or ZY;
R is aryl, aryl lower alkyl, such as benzyl, wherein the
aryl group is unsubstituted or substituted and R_1 is
lower alkyl. In this embodiment, it is most preferred
20 that R_3 is hydrogen, an alkyl group, especially methyl,
substituted by electron donating group, such as lower
alkoxy, (e.g., methoxy, ethoxy and the like), NR_4OR_5 or
 ONR_4R_7 , wherein these groups are defined hereinabove.

The most preferred compounds utilized are those
25 of the formula:



30 wherein

Ar is aryl, especially phenyl, which is
unsubstituted or substituted with at least one electron
donating group or electron withdrawing group;

35 R_1 is lower alkyl; and

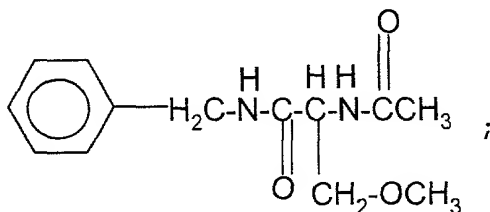
5 R_3 is as defined herein, but especially
hydrogen, loweralkyl, which is unsubstituted or
substituted by at least an electron donating group or
electron withdrawing group or ZY. It is even more
preferred that R_3 is, in this embodiment, hydrogen, an
10 alkyl group which is unsubstituted or substituted by an
electron donating group, such as alkoxy, or NR_4OR_5 or
 ONR_4R_7 . It is most preferred that R_3 is CH_2-Q , wherein Q
is lower alkoxy, NR_4OR_5 or ONR_4R_7 , wherein R_4 is hydrogen or
alkyl containing 1-3 carbon atoms, R_5 is hydrogen or
15 alkyl containing 1-3 carbon atoms, and R_7 is hydrogen or
alkyl containing 1-3 carbon atoms.

The preferred R_1 is CH_3 .

The most preferred aryl is phenyl.

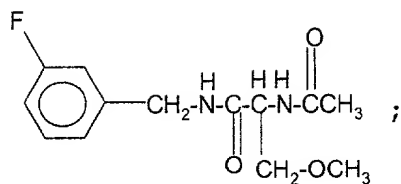
The most preferred compounds include:

20 (R) -N-Benzyl-2-acetamido-3-methoxy-
propionamide,

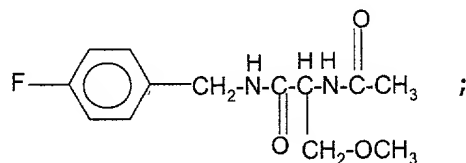


25
30 O-methyl-N-acetyl-D-serine-m-fluorobenzyl-
amide,

5

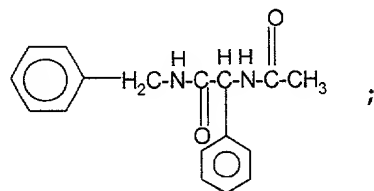


10 O-methyl-N-acetyl-D-serine-p-fluorobenzylamide,



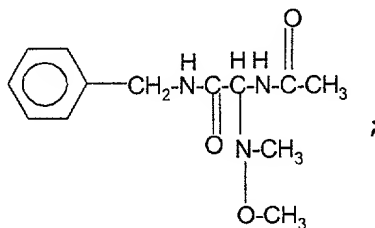
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N-acetyl-D-phenylglycinebenzylamide;



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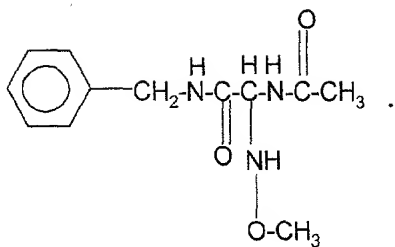
25 D-1,2-(N, O-dimethylhydroxylamino)-2-acetamide acetic acid benzylamide,



30

D-1,2-(O-methylhydroxylamino)-2-acetamido acetic acid benzylamide,

5



10

Some of the preferred compounds are described in U.S.
 Patent No. 5,773,475, the contents of which are
 incorporated by reference.

15

20

It is to be understood that the various
 combinations and permutations of the Markush groups of R_1 ,
 R_2 , R_3 , R and n described herein are contemplated to be
 within the scope of the present invention. Moreover, the
 present invention also encompasses compounds and
 compositions which contain one or more elements of each of
 the various Markush groupings in R_1 , R_2 , R_3 , n and R and the
 various combinations thereof. Thus, for example, the
 present invention contemplates that R_1 may be one or more
 of the substituents listed hereinabove in combination with
 any and all of the substituents of R_2 , R_3 , and R with
 respect to each value of n .

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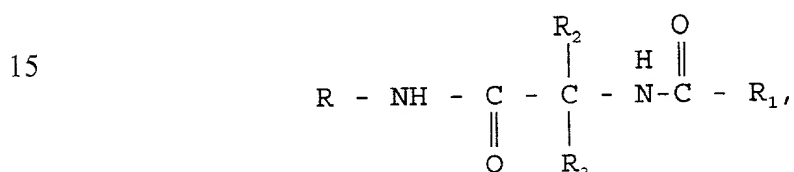
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The compounds utilized in the present invention
 may contain one (1) or more asymmetric carbons and may
 exist in racemic and optically active forms. The
 configuration around each asymmetric carbon can be either
 the D or L form. (It is well known in the art that the
 configuration around chiral carbon atoms can also be
 described as R or S in the Cahn-Prelog-Ingold nomenclature

5 system). All of the various configurations around each asymmetric carbon, including the various enantiomers and diastereomers as well as racemic mixtures and mixtures of enantiomers, diastereomers or both are contemplated by the present invention.

10 In the principal chain, there exists asymmetry at the carbon atom to which the groups R_2 and R_3 are attached. When n is 1, the compounds of the present invention are of the formula



20 wherein R , R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , Z and Y are as defined previously.

As used herein, the term configuration shall refer to the configuration around the carbon atom to which R_2 and R_3 are attached, even though other chiral
25 centers may be present in the molecule. Therefore, when referring to a particular configuration, such as D or L, it is to be understood to mean the D or L stereoisomer at the carbon atom to which R_2 and R_3 are attached. However, it also includes all possible enantiomers and
30 diastereomers at other chiral centers, if any, present in the compound.

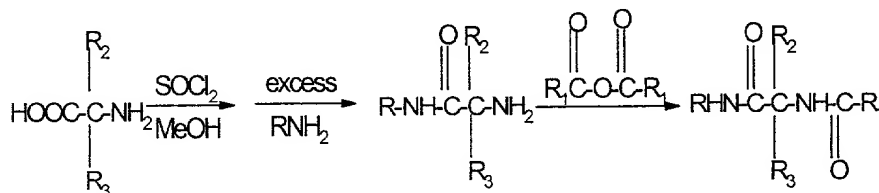
The compounds of the present invention are directed to all the optical isomers, i.e., the compounds of the present invention are either the L-stereoisomer or
35 the D-stereoisomer (at the carbon atom to which R_2 and R_3 are attached). These stereoisomers may be found in

5 mixtures of the L and D stereoisomer, e.g., racemic mixtures. The D stereoisomer is preferred.

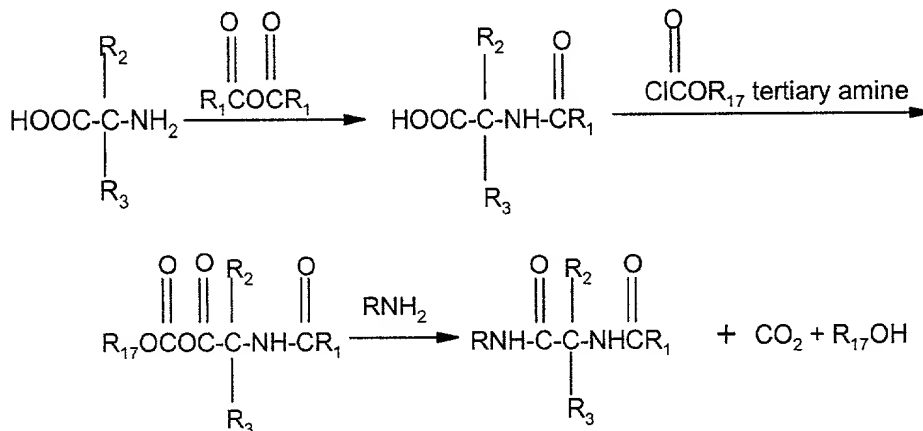
Depending upon the substituents, the present compounds may form addition salts as well. All of these forms are contemplated to be within the scope of this invention, including mixtures of the stereoisomeric forms.

The following three schemes of preparation are generally exemplary of the process of which can be employed for the preparation of the compounds utilized. These are described in U.S. Patent Nos. 5,378,729 and 5,773,475, the contents of both of which are incorporated by reference.

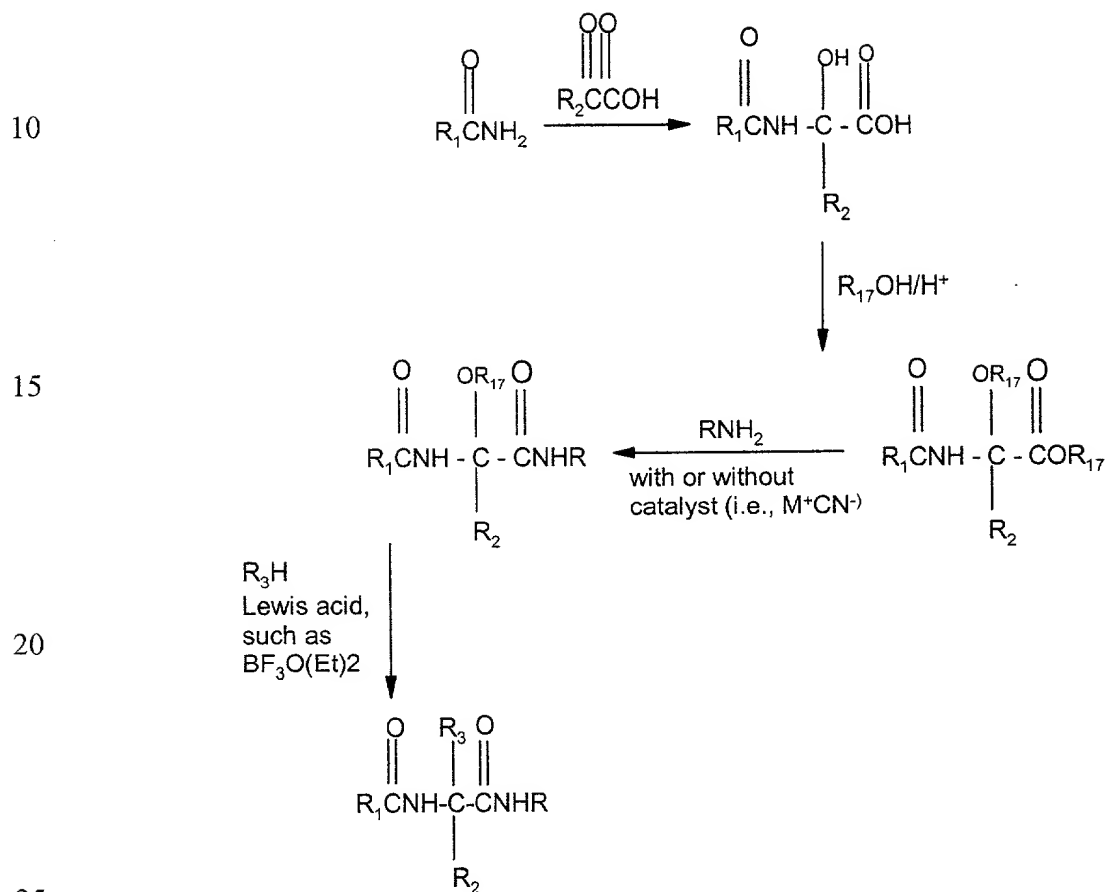
Scheme I



Scheme II



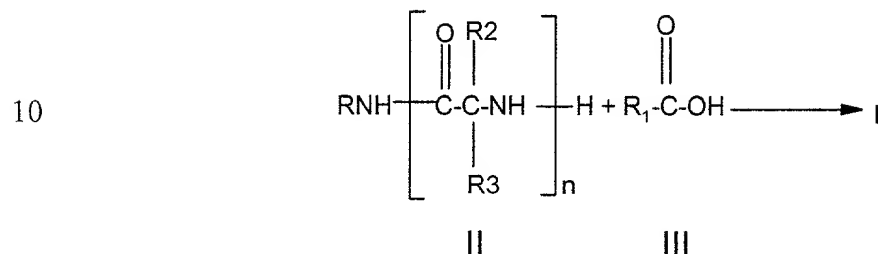
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Scheme III

wherein R_1 , R_2 , R_3 and are as defined hereinabove and R_{17} is lower alkyl, aryl or lowerarylalkyl.

30 More specifically, these compounds can be prepared by art-recognized procedures from known compounds or readily preparable intermediates. For instance, compounds of Formula I can be prepared by reacting amines of Formula II with an acylating

5 derivative of a carboxylic acid of Formula III under
amide forming conditions:

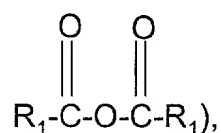


15 wherein R, R₁, R₂, R₃ and n are as defined hereinabove,
although it is preferred that n is 1.

The amide forming conditions referred to herein
involve the use of known derivatives of the described
acids, such as the acyl halides, (e.g.



25 wherein X is Cl, Br and the like), anhydrides (e.g.,



30 mixed anhydrides, or lower alkyl esters, and the like.
It is preferred that the acylating derivative used is the
anhydride. When alkyl esters are employed, amide bond
formation can be effected by metal cyanides such as
sodium or potassium cyanides.

5 Another exemplary procedure for preparing
compounds wherein at least one of R_2 and R_3 is aromatic or
heteroaromatic is depicted in Scheme IV.

 The ester (IV) is reacted with halogen and
ultraviolet light in the presence of a catalyst, e.g.,
10 AIBN, to form the halo derivative (V). (V) is reacted in
the presence of a Lewis acid, such as zinc chloride, with
an aromatic or heteroaromatic compound to form the
compound (VI). (VI) in turn is hydrolyzed and then
reacted with alkylhaloformate, such as
15 alkylchloroformate, in the presence of a tertiary amine
to generate the mixed N-acyl amino acid carbonic ester
anhydride (VIII). This intermediate is reacted with an
amine under amide forming conditions to give the compound
of Formula I. Alternatively, (VI) can be reacted
20 directly with an amine (RNH_2), optionally in the presence
of a metal catalyst, such as metal cyanides, e.g.,
potassium or sodium cyanide, under amide forming
conditions to form a compound of Formula I.
Alternatively, compound VIII can be prepared by an
25 independent method and converted to VI which is then
reacted with an amine, with or without catalyst, to form
the compound of Formula I.

5

Scheme IV

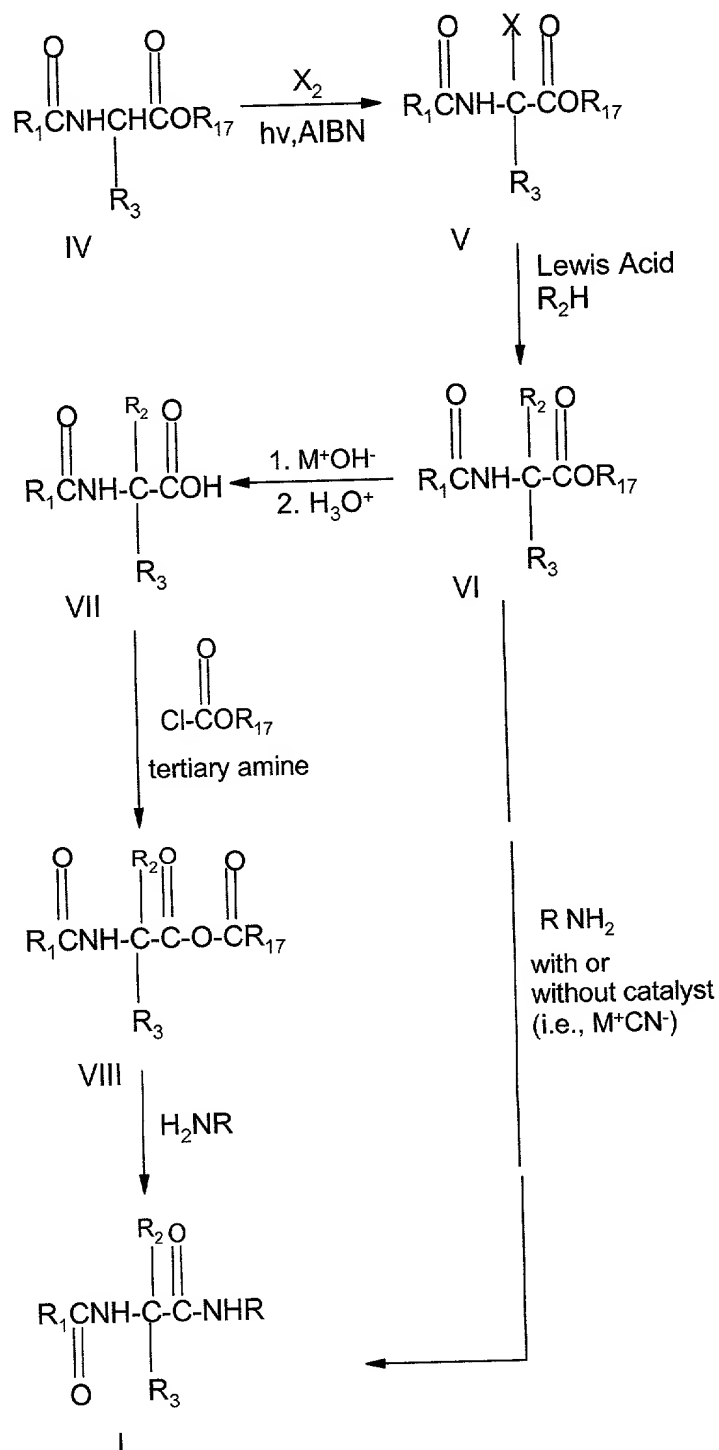
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5

wherein $X = \text{halogen (i.e., Cl, Br)}$;

$R_{17} = \text{lower alkyl, aryl, or aryl lower alkyl}$;

and

10

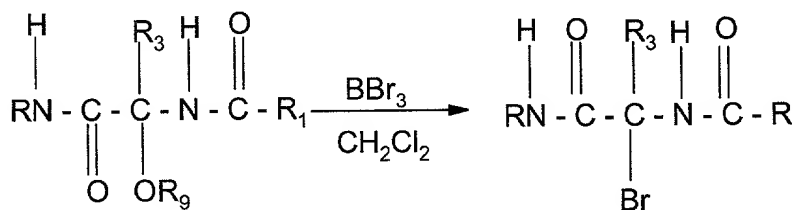
$M^+ = \text{metal cation (i.e., Na}^+, \text{K}^+)$

Two additional synthetic routes may be employed for the preparation of compounds wherein R_2 or R_3 is Z-Y as defined hereinabove. In one scheme, for the preparation of these complexes, a substitution reaction is used:

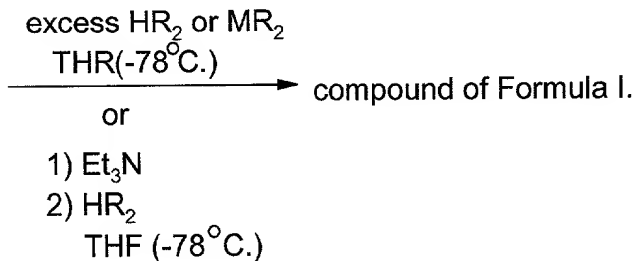
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Scheme V

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25



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In the above scheme, R_3 is lower alkyl, R_2 is Z-Y and Z, Y, R, R_3 and R_1 are as defined hereinabove and M is a metal.

5 The ether functionality on IX can be cleaved by
treatment with Lewis acids, such as BBr_3 , in an inert
solvent such as methylene chloride to form the
corresponding halo (bromo) derivative. Addition of
10 either an excess of H-R_2 or MR_2 or the sequential addition
of triethylamine and H-R_2 to a THF mixture containing the
halo derivative furnishes the desired product. For
example, in the case wherein the compound of Formula IX
is 2-acetamido-N-benzyl-2-ethoxy acetamide, its treatment
with BBr_2 in CH_2Cl_2 led to the formation of the α -bromo
15 derivative, 2-acetamido-N-benzyl-2-bromoacetamide.
Addition of an excess of HR_2 or the sequential addition
of triethylamine and HR_2 to the THF mixture containing
the bromo adduct furnishes the desired product.

20 In another procedure, the product wherein R_2 or
 R_3 is Z-Y can also be prepared by a substitution reaction
on a quaternary ammonium derivative of the compound of
Formula I as outlined below:

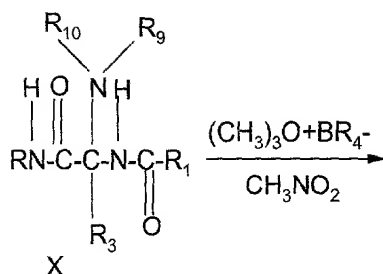
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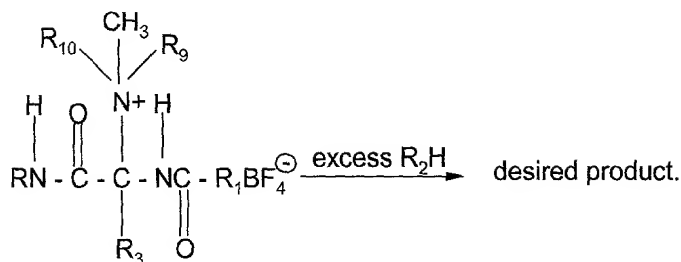
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Scheme VI

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In scheme VI, R, R₁, R₃ and R are as defined hereinabove, R₂ is Z-Y and R₉ and R₁₀ are independently lower alkyl. In scheme VI, methylation of compound X with a methylation reagent, such as trimethyloxonium tetrafluoroborate, provided the corresponding ammonium derivative.

Subsequent treatment of the ammonium salt with HR₂ furnishes the desired product. For example, methylation of 2-acetamido-N-benzyl-2-(N,N-dimethylamino) acetamide with trimethyloxonium tetrafluoroborate in nitromethane furnished the quaternary ammonium derivative, 2-acetamido-N-benzyl-(N,N,N-trimethylammonium) acetamide tetrafluoroborate in high yields. Subsequent treatment of the salt with the HR₂ reagent in the methanol leads to the production of the desired product.

As in any organic reaction, inert solvents can be employed such as methanol, ethanol, propanol, acetone,

5 tetrahydrofuran, dioxane, dimethylformamide,
dichloromethane, chloroform and the like. The reaction
is normally effected at or near room temperature,
although temperatures from 0° C. up to the reflux
temperature of the solvent can be employed.

10 As a further convenience, the amide forming
reaction can be effected in the presence of a base, such
as a tertiary organic amine, e.g., triethylamine,
pyridine, 4-methyl-morpholine, picolines and the like,
particularly where hydrogen halide is formed by the amide
15 forming reaction, e.g., the reaction of an acyl halide
and the amine of Formula II. Of course, in those
reactions where hydrogen halide is produced, any of the
commonly used hydrogen halide acceptors can also be used.

20 The exact mineral acid or Lewis acid employed
in the reaction will vary depending on the given
transformation, the temperature required for the
conversion and the sensitivity of the reagent toward the
acid in the reaction mixture.

25 The various substituents, e.g., as defined in
R, R₁, R₂, and R₃, can be present in the starting
compounds, added to any one of the intermediates or added
after formation of the final products by the known
methods of substitution or conversion reactions. For
example, the nitro groups can be added to the aromatic
30 ring by nitration and the nitro group converted to other
groups, such as amino by reduction, and halo by
diazotization of the amino group and replacement of the
diazo group. Alkanoyl groups can be substituted onto the
aryl groups by Friedel-Crafts acylation. The acyl groups

5 can be then transformed to the corresponding alkyl groups
by various methods, including the Woff-Kishner reduction
or Clemmenson reduction. Amino groups can be alkylated
to form mono, dialkylamino and trialkylamino groups; and
mercapto and hydroxy groups can be alkylated to form
10 corresponding thioethers or ethers, respectively.
Primary alcohols can be oxidized by oxidizing agents
known in the art to form carboxylic acids or aldehydes,
and secondary alcohols can be oxidized to form ketones.
Thus, substitution or oxidation reactions or a
15 combination thereof can be employed to provide a variety
of substituents throughout the molecule of the starting
material, intermediates, or the final product.

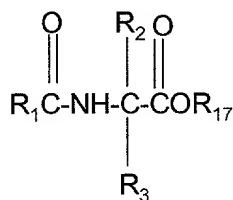
In the above reactions, if the substituents
themselves are reactive, then the substituents can
20 themselves be protected according to techniques known in
the art. A variety of protecting groups known in the art
may be employed. Examples of many of these possible
groups may be found in "Protective Groups in Organic
Synthesis," by T.W. Greene, John Wiley & Sons, 1981.

25 Resulting mixtures of isomers can be separated
into the pure isomers by methods known to one skilled in
the art, e.g., by fractional distillation,
crystallization and/or chromatography.

The compounds obviously exist in stereoisomeric
30 forms and the products obtained thus can be mixtures of
the isomers, which can be resolved. Optically pure
functionalized amino acid derivatives can be prepared
directly from the corresponding pure chiral intermediate.
Racemic products can likewise be resolved into the

5 optical antipodes, for example, by separation of
diastereomeric salts thereof, e.g., by fractional
crystallization, by selective enzymatic hydrolysis, e.g.,
papain digestion, or by use of a chiral stationary phase
10 in a chromatographic separation, such as by high pressure
liquid chromatography (HPLC). For a discussion of chiral
stationary phases for HPLC, See, DeCamp, Chirality, 1, 2-
6 (1989), which is incorporated herein by reference with
the same force and effect as is fully set forth herein.

For example, a racemic mixture of an
15 intermediate in any of the schemes depicted hereinabove
has the formula:



wherein R_{17} is H (which can be prepared according to the
25 procedures of Schemes 1, 2, 3 or 4) is reacted with an
optically active amine, RNH_2 , e.g., (R)(+) α -methyl-
benzylamine, to form a pair of diastereomeric salts.
Diastereomers can then be separated by recognized
techniques known in the art, such as fractional
30 recrystallization and the like.

In another method, a racemic mixture of final
products or intermediates can be resolved by using
enzymatic methods. Since enzymes are chiral molecules,
it can be used to separate the racemic modification,

5 since it will preferentially act on one of the compounds,
without affecting the enantiomer. For example, acylase,
such as acylase I, can be used to separate the racemic
modification of an intermediate D, L (\pm) α -acetamido-2-
furanacetic acid. It acts on the L(\pm) α -acetamido-2-
10 furanacetic acid, but will not act on the D enantiomer.
In this way, the D(-) α -acetamido-2-furanacetic acid can
be isolated. The intermediate can then react with the
amine (RNH₂) under amide forming conditions as described
hereinabove to form the compound of Formula I.

15 The compounds utilized in the present invention
are useful as such as depicted in the Formula I or can be
employed in the form of salts in view of its basic nature
by the presence of the free amino group. Thus, the
compounds of Formula I form salts with a wide variety of
20 acids, inorganic and organic, including pharmaceutically
acceptable acids. The salts with therapeutically
acceptable acids are of course useful in the preparation
of formulations where enhanced water solubility is most
advantageous.

25 These pharmaceutically acceptable salts have
also therapeutic efficacy. These salts include salts of
inorganic acids such as hydrochloric, hydroiodic,
hydrobromic, phosphoric, metaphosphoric, nitric acid and
sulfuric acids as well as salts of organic acids, such as
30 tartaric, acetic, citric, malic, benzoic, perchloric,
glycolic, gluconic, succinic, aryl sulfonic, (e.g., p-
toluene sulfonic acids, benzenesulfonic), phosphoric,
malonic, and the like.

5

It is preferred that the compound utilized in the present invention is used in therapeutically effective amounts.

10

The physician will determine the dosage of the present therapeutic agents which will be most suitable and it will vary with the form of administration and the particular compound chosen, and furthermore, it will vary with the patient under treatment, the age of the patient, and the type of malady being treated. He will generally wish to initiate treatment with small dosages

15

substantially less than the optimum dose of the compound and increase the dosage by small increments until the optimum effect under the circumstances is reached. The compounds are useful in the same manner as comparable therapeutic agents and the dosage level is of the same order of magnitude as is generally employed with these other therapeutic agents.

20

In a preferred embodiment, the compounds utilized are administered in amounts ranging from about 1 mg to about 100 mg per kilogram of body weight per day. This dosage regimen may be adjusted by the physician to provide the optimum therapeutic response. For example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation. The compounds of Formula I may be administered in a convenient manner, such as by oral, intravenous (where water soluble), intramuscular or subcutaneous routes.

25

30

The compounds of Formula I may be orally administered, for example, with an inert diluent or with

5 an assimilable edible carrier, or it may be enclosed in
hard or soft shell gelatin capsules, or it may be
compressed into tablets, or it may be incorporated
directly into the food of the diet. For oral therapeutic
administration, the active compound of Formula I may be
10 incorporated with excipients and used in the form of
ingestible tablets, buccal tablets, troches, capsules,
elixirs, suspensions, syrups, wafers, and the like. Such
compositions and preparations should contain at least 1%
of active compound of Formula I. The percentage of the
15 compositions and preparations may, of course, be varied
and may conveniently be between about 5 to about 80% of
the weight of the unit. The amount of active compound of
Formula I in such therapeutically useful compositions is
such that a suitable dosage will be obtained. Preferred
20 compositions or preparations according to the present
invention contains between about 10 mg and 6 g of active
compound of Formula I.

The tablets, troches, pills, capsules and the
like may also contain the following: a binder such as gum
25 tragacanth, acacia, corn starch or gelatin; excipients
such as dicalcium phosphate; a disintegrating agent such
as corn starch, potato starch, alginic acid and the like;
a lubricant such as magnesium stearate; and a sweetening
agent such as sucrose, lactose or saccharin may be added
30 or a flavoring agent such as peppermint, oil of
wintergreen, or cherry flavoring. When the dosage unit
form is a capsule, it may contain, in addition to
materials of the above type, a liquid carrier.

5 Various other materials may be present as
coatings or otherwise modify the physical form of the
dosage unit. For instance, tablets, pills, or capsules
may be coated with shellac, sugar or both. A syrup or
10 elixir may contain the active compound, sucrose as a
sweetening agent, methyl and propylparabens as
preservatives, a dye and flavoring such as cherry or
orange flavor. Of course, any material used in preparing
any dosage unit form should be pharmaceutically pure and
substantially non-toxic in the amounts employed. In
15 addition, the active compound may be incorporated into
sustained-release preparations and formulations. For
example, sustained release dosage forms are contemplated
wherein the active ingredient is bound to an ion exchange
resin which, optionally, can be coated with a diffusion
20 barrier coating to modify the release properties of the
resin.

 The active compound may also be administered
parenterally or intraperitoneally. Dispersions can also
be prepared in glycerol, liquid polyethylene glycols, and
25 mixtures thereof, and in oils. Under ordinary conditions
of storage and use, these preparations contain a
preservative to prevent the growth of microorganisms.

 The pharmaceutical forms suitable for
injectable use include sterile aqueous solutions (where
30 water soluble) or dispersions and sterile powders for the
extemporaneous preparation of sterile injectable
solutions or dispersions. In all cases, the form must be
sterile and must be fluid to the extent that easy
syringability exists. It must be stable under the

5 conditions of manufacture and storage and must be
preserved against the contaminating action of
microorganisms such as bacteria and fungi. The carrier
can be a solvent or dispersion medium containing, for
example, water, ethanol, polyol (for example, glycerol,
10 propylene glycol, and liquid polyethylene glycol, and the
like), suitable mixtures thereof, and vegetable oils.
The proper fluidity can be maintained, for example, by
the use of a coating such as lecithin, by the maintenance
of the required particle size, in the case of
15 dispersions, and by the use of surfactants. The
prevention of the action of microorganisms can be brought
about by various antibacterial and antifungal agents, for
example, parabens, chlorobutanol, phenol, sorbic acid,
thimerosal, and the like. In many cases, it will be
20 preferable to include isotonic agents, for example,
sugars or sodium chloride. Prolonged absorption of the
injectable compositions can be brought about by the use
in the compositions of agents delaying absorption, for
example, aluminum monostearate and gelatin.

25 Sterile injectable solutions are prepared by
incorporating the active compound in the required amount
in the appropriate solvent with various other ingredients
enumerated above, as required, followed by filtered
sterilization. Generally, dispersions are prepared by
30 incorporating the various sterilized active ingredients
into a sterile vehicle which contains the basic
dispersion medium and the required other ingredients from
those enumerated above. In the case of sterile powders
for the preparation of sterile injectable solutions, the

5 preferred methods of preparation are the use of vacuum
drying and freeze-drying techniques on the active
ingredient plus any additional desired ingredients from
previously sterile-filtered solution(s) thereof.

10 As used herein, "pharmaceutically acceptable
carrier" includes any and all solvents, dispersion media,
coatings, antibacterial and antifungal agents, isotonic
and absorption delaying agents for pharmaceutical active
substances which are well known in the art. Except
15 insofar as any conventional media or agent is
incompatible with the active ingredient, its use in the
therapeutic compositions is contemplated. Supplementary
active ingredients can also be incorporated into the
compositions.

20 It is especially advantageous to formulate
parenteral compositions in dosage unit form for ease of
administration and uniformity of dosage. Dosage unit
form as used herein refers to physically discrete units
suited as unitary dosages for the mammalian subjects to
be treated; each unit containing a predetermined quantity
25 of active material calculated to produce the desired
therapeutic effect in association with the required
pharmaceutical carrier. The specifics for the novel
dosage unit forms of the invention are dictated by and
directly dependent on (a) the unique characteristics of
30 the active material and the particular therapeutic effect
to be achieved, and (b) the limitations inherent in the
art of compounding such as active material for the
treatment of disease in living subjects having a diseased

5 condition in which bodily health is impaired as herein disclosed in detail.

The principal active ingredient is compounded for convenient and effective administration in effective amounts with a suitable pharmaceutically acceptable
10 carrier in dosage unit form as hereinbefore described. A unit dosage can, for example, contain the principal active compound in amounts ranging from about 10 mg to about 6 g. Expressed in proportions, the active compound is generally present from about 1 to about 750 mg/ml of
15 carrier. In the case of compositions containing supplementary active ingredients, the dosages are determined by reference to the usual dose and manner of administration of the said ingredients.

As used herein the term "patient" or "subject"
20 refers to a warm blooded animal, preferably mammals, such as, for example, cats, dogs, horses, cows, pigs, mice, rats and primates, including humans. The preferred patient is human.

The term "treat" refers to either relieving the
25 pain associated with a disease or condition or alleviating the patient's disease or condition.

The compounds of the present invention are useful for treating chronic pain. As used herein, the term "chronic pain" is defined as pain persisting for an
30 extended period of time, for example, greater than three to six months, although the characteristic signs described hereinbelow can occur earlier or later than this period. Vegetative signs, such as lassitude, sleep

5 disturbances, decreased appetite, loss of taste or food,
weight loss, diminished libido and constipation develop.

A type of chronic pain that the compounds of
the present invention are especially useful in treating
is nociceptive pain and neuropathic pain. As used
10 herein, "nociceptive pain" is pain that is judged to be
commensurate with on-going activation of pain-sensitive
somatic or visceral nerve fibers. This pain is typically
experienced as aching or pressure-like when somatic
nerves are involved.

15 On the other hand, neuropathic pain is caused
by damage to nerve tissue. The pain may result from
nervous system damage involving reorganization of central
somato-sensory processing, i.e., differentiation pains
(those due to partial or complete interruption of
20 peripheral or central afferent neural activity) and those
dependent on sympathetic-mediated pains (those dependent
on efferent sympathetic activity). Alternatively, the
pain may result from on-going peripheral processes or
pathology, such as nerve compression or neuroma
25 formation.

The pain associated with these neuropathic
pains is a deep pain, i.e., a spontaneous burning pain
often accompanied by a superimposed lancinating
component. Other pain sensations, such as hyperesthesia,
30 hyperalgesia, allodynia (pain from a non-noxious
stimulant) and hyperpathia (particularly unpleasant,
exaggerated pain response) may also be felt by the
patient experiencing neuropathic pain.

5 The compounds of the present invention are administered to a patient suffering from neuropathic pain in an analgesic effective amount. These amounts are equivalent to the therapeutically effective amounts described hereinabove.

10 Another type of malady experienced by patients for which the compounds of Formula I are useful in treating is headaches, especially migraine headaches.

15 A migraine headache is a paroxysmal disorder characterized by recurrent attacks of headaches, which may be associated with visual or GI disturbances. In migraine headaches, the pain is usually generalized, but it may also be a unilateral throbbing, which begins around one of the eyes and then spreads through the head to involve one or both sides.

20 In some severe cases, it is accompanied by anorexia, nausea and vomiting and photophobia. In addition, the extremities are cold and cyanosed, and the patient is irritable. Moreover, the scalp arteries are prominent and their amplitude of pulsation is increased.

25 The compounds of Formula I are useful in the prophylaxis and the treatment of migraine headaches and alleviating the pain associated therewith. They are administered to patients with migraine headaches in pain relieving effective amounts. These amounts are
30 equivalent to the therapeutically effective amounts described hereinabove. The discussions associated with therapeutic effective amounts are applicable to the treatment and/or prophylaxis of migraine headaches and are incorporated herein.

5 The compounds of the present invention are also
useful in treating patients with bipolar disorders.
Bipolar disorders commonly originate with depression and
are characterized by at least one elated period during
the course of the illness. In bipolar I disorder, major
10 depressive episodes and full-blown manic alternate. In
bipolar II disorder, depressive episodes alternate with
hypomanias (i.e., mild, non-psychotic periods of
excitement) of relatively short duration. These
disorders are typically accompanied by the subject
15 experiencing hypersomnia and overeating and these traits
may recur on a seasonal basis. Additionally, the patient
may suffer from insomnia and poor appetite.

In the full blown bipolar disorder, the mood of
the person suffering therefrom is usually elation, but
20 irritability and frank hostility and cantankerousness are
also common. The patient is morbid, yet the patient
believes that he is in the best mental state. He is
psychotic, impatient, intrusive, meddlesome and responds
with aggressive irritability when challenged or crossed.
25 The patient may experience interpersonal friction and he
may have secondary paranoid delusional interpretations of
being persecuted. The patient usually suffers from
delusions, especially grand delusions, e.g., false belief
of personal wealth, power, inventiveness, genius or
30 importance. The patient may believe that he is being
assaulted or persecuted by others. He may even suffer
from hallucinations. In the extreme, the psychomotor
activity is so frenzied that any understandable link
between mood and behavior is lost (delirious mania).

5 The present compounds are also useful for
treating cyclothymic disorders.

 The term bipolar disorders, as used herein,
also includes mixed states which are rapid alternation
between depression and manic manifestations, as for
10 example, momentary switching into tearfulness and
suicidal ideas.

 The amounts effective for treating bipolar
disorders are the therapeutically effective amounts
described hereinabove. The discussions associated with
15 therapeutic effective amounts are applicable to the
treatment of bipolar disorders and are incorporated
herein by reference.

 The compounds of the present invention are
useful in treating various types of neuroses, especially
20 obsessive-compulsive neurosis.

 The former, by definition, is a disorder
characterized by the presence of ideas and fantasies
which are recurrent, in fact obsessive and by repetitive
impulses or actions (compulsions) that the patient
25 recognizes as morbid and toward which he feels a strong
inner resistance. The patient himself is anxious, but
the anxiety arises in response to internally derived
thoughts and disorders that the patient fears he may
execute despite a desire to restrain himself.

30 Again, the amounts described herein are
therapeutically effective amounts, which discussions are
incorporated herein by reference.

 Without wishing to be bound, the compounds of
the present invention are believed to interact with the

5 strychnine-insensitive glycine site of the NMDA receptor.
By "interact", it is meant that the compounds may be NMDA
antagonists, NMDA agonists or partial
agonists/antagonists.

10 The NMDA (N-methyl-D-aspartate) receptor is one
of the three major sub-types of glutamate receptors in
the CNS. Glutamate, which is believed to be the major
excitatory neurotransmitter in the brain, activates the
NMDA receptor. The NMDA receptors are found in the
membranes of virtually every neuron in the brain. NMDA
15 receptors are ligand gated cation channels that allow
 Na^+ , K^+ , and Ca^{+2} to permeate when they are activated by
glutamate, aspartate or NMDA.

20 However, glutamate alone cannot activate the
NMDA receptor. In order to become fully activated by
glutamate, the NMDA receptor channel must bind glycine at
a specific, high affinity glycine binding site that is
separate from the glutamate/NMDA binding site of the
receptor protein. Glycine is therefore an obligatory co-
agonist at the NMDA receptor/channel complex.

25 In addition to the binding site for
glutamate/NMDA and glycine, the NMDA receptor carries a
number of other functionally important binding sites,
e.g., Mg^{2+} , Zn^{2+} , polyamines, arachidonic acid and
phencyclidine (PCP).

30 Without wishing to be bound, it is thus
believed that functional modulation of the NMDA subclass
of glutamate receptors can be achieved through actions at
different recognition sites such as: the primary
transmitter site (competitive), the phencyclidine (PCP)

5 site located inside the cation channel (uncompetitive),
the polyamine modulatory site, and the strychnine -
insensitive glycine site (glycine_b).

Without wishing to be bound, it is believed
that the compounds of the present invention interact with
10 the glycine binding site of the NMDA receptor. For
example, the compounds of the present invention may be
antagonists of the glycine binding site of the NMDA
receptor.

Glycine is a co-agonist at NMDA receptors and
15 its presence at moderate nM concentrations is a
prerequisite for channel activation by glutamate or NMDA.
D-serine is also known as an endogenous agonist for the
glycine_b receptors. In fact, the D-isomers of serine and
alanine are nearly as potent as glycine and considerably
20 more potent than the L-isomers; and these also modulate
the glycine_b site. Larger amino acids are less
effective. Cycloserine shows up as a relatively potent
glycine agonist at the NMDA receptor complex site.

Although a number of uncompetitive and
25 competitive NMDA receptor antagonists are already used
clinically or are at advanced stages of development, less
is known about the therapeutic potential of antagonists
at the glycine_b site. Initial preclinical evidence
suggests that a different, perhaps more promising,
30 therapeutic profile can be expected from glycine_b
antagonism. The glycine_b antagonists have been reported
to lack many of the side effects classically associated
with NMDA receptor blockade such as: 1) lack of
neurodegenerative changes in the cingulate/retrosplenial

5 cortex; 2)lack of psychotomimetic-like effects, and
3)lack of learning impairing effects at anticonvulsive
doses. However, more recently some full glycine_b
antagonists, have also been reported to have good
therapeutic indices following systemic administration as
10 neuroprotective agents in models of focal ischemia; and
trauma, as antiepileptics, even in models of partial
complex seizures; as anxiolytics; as
antipsychotomimetics; in blocking spreading depression;
and in models of hyperalgesia.

15 The compounds of the present invention exhibit
no specific affinity for a standard battery of CNS and
peripheral receptors, including many subtypes of
glutamate receptors. However, they do exhibit affinity
at the glycine strychnine-insensitive site of the NMDA
20 receptor complex. For example, utilizing a
representative compound, (R)-2-Acetamido-N-benzyl-3-
methoxy propionamide, the present inventor has determined
that the affinity thereof at the glycine-strychnine-
insensitive site of the NMDA receptor complex has a IC₅₀
25 value of 5.3 uM using dichlorokynurenic acid as the
ligand. Moreover, other studies have indicated that the
proactive effects of this representative compound on
threshold extension in rats can be reversed by D-serine,
a glycine agonist, in a dose dependent fashion. Thus the
30 compounds of the present invention are believed, without
wishing to be bound, to be mediated by its interaction
with the glycine_b/D-serine site.

However, the compounds of the present invention
exhibit little or no side effects caused by non-selective

5 binding with other receptors, particularly the PCP
binding site of the NMDA receptor and the glutamate
binding site of the NMDA receptor.

There is an endogenous ligand present that
binds to the glycine_b site. Some believe that it is
10 glycine, while others believe that it is D-serine. See
Snyder, et al., Am. J. Psychiatry, 2000, 157, 11 1738-
1751; and Baranano, et al., Trends in Neurosciences, 2001,
24, 99-106.

Without wishing to be bound, it is believed
15 that the compounds of the present invention modulate the
activity of the glycine_b receptor. Moreover, without
wishing to be bound, it is believed that the compounds of
the present invention are useful for the treatment of
conditions associated with or caused by abnormal receptor
20 activity at the glycine_b receptor site. Without wishing
to be bound, it is believed that compounds of the present
invention interact with this glycine_b receptor site on
the NMDA receptor.

Without wishing to be bound, it is believed
25 that by interacting at the strychnine-insensitive glycine
site on the NMDA receptors, the compounds of Formula I
are useful in treating or preventing neuronal loss,
neurodegenerative diseases and chronic pain. In addition
they are also anti-psychotics.

30 Other neurodegenerative diseases which are
treated with the compounds of Formula I are Alzheimer's
disease, Huntington's disease and Down's syndrome.

The compounds described herein also are useful
for treating or preventing dementia.

5 Besides treating neuropathic pain, the
compounds of the present invention find utility in
treating or preventing pain, e.g., chronic pain. Such
chronic pain can result from surgery, trauma, headache,
arthritis, pain associated with a terminal case of
10 cancer, or degenerative diseases. The compounds of
Formula I find utility in the treatment of phantom pain
that results from amputation of an extremity.

 In addition, it is believed, without wishing to
be bound, that the strychnine-insensitive glycine site of
15 the NMDA receptors is involved in the development of
persistent pain following nerve and tissue injury.
Tissue injury, such as that caused by injecting a small
amount of formalin subcutaneously into the hindpaw of a
test animal, has been shown to produce an immediate
20 increase of glutamate and aspartate in the spinal cord.
Without wishing to be bound, it is believed that the
administration of the compounds of the present invention
reduces the response of spinal cord dorsal horn neurons
following formalin injection. These dorsal horn neurons
25 are critical in carrying the pain signal from the spinal
cord to the brain and a reduced response of these neurons
is indicative of a reduction in pain perceived by the
test animal to which pain has been inflicted by
subcutaneous formalin injection.

30 Because the compounds of the present invention
block dorsal horn neuron response induced by subcutaneous
formalin injection, they are useful for the treatment of
chronic pain, such as pain caused by surgery or by

5 amputation (phantom pain) or by infliction of other
wounds (wound pain).

The degree of pain is determined by measuring
the decrease in the amount of time the animal spends
licking the formalin-injected paw after administration of
10 the drug.

Compared to vehicle control, the
intraperitoneal injection of the putative glycine
receptor modulators of the present invention 30 minutes
prior to formalin injection into the hindpaw
15 significantly inhibits formalin-induced chronic pain in a
dose-dependent manner as determined by the reduction of
the time spent by the mouse licking the formalin injected
hindpaw. This is shown in Example 2 hereinbelow.

In the following Examples 1-5, the following
20 were used:

1. Animals

Male or female ICR mice and male or female Long
Evans rats provided by animal breeding center of MDS
Panlabs Taiwan, Ltd. were used. Space allocation for
25 animals was as follows: 45x23x15 cm for 10 mice, 45x23x15
cm for 6 rats. Mice and rats were housed in APEC®
(Allentown Gaging, Allentown, NJ 08501, U.S.A.) cages in
a positive pressure isolator (NuAire®, Mode: Nu-605,
airflow velocity 50 ± 5 ft/min, HEPA Filter). All
30 animals were maintained in a controlled temperature (22°C
- 24°C) and humidity (60% - 80%) environment with 12 hour
light dark cycles for at least one week in MDS Panlabs
Taiwan laboratory prior to being used. Free access to
standard lab chow for mice and rats (Fwusow Industry Co.,

5 Limited, Taiwan) and tap water was granted. All aspects
of this work including housing, experimentation and
disposal of animals were performed in general accordance
with the International Guiding Principles for Biomedical
Research Involving Animals (CIOMS Publication No. ISBN
10 90360194, 1985).

2. Chemicals

The chemicals used were Acetic Acid (Sigma,
U.S.A.), Aspirin (ICN Biomedicals Inc.), CGS-19755 (RBI,
15 U.S.A.), Diazepam (Sigma, U.S.A.), Formalin (Wako,
Japan), Morphine (National Narcotics Bureau of Taiwan),
NMDA (Sigma, U.S.A.), Phenylquionone (Sigma, U.S.A.) and
Saline (Astar, Taiwan).

20 3. (R)-N-Benzyl-3-Acetamido-3-
methoxypropionamide was prepared in accordance with the
procedure in U.S. Patent No. 5,773,475. In the following
examples, it will be designated as Compound I.

The following experiments illustrate the
25 effectiveness of the compounds in treating pain. In the
first series of experiments, a representative compound of
the present invention, (R)-2-Acetamido-N-benzyl-3-
methoxypropionamide (CMPD I) was utilized at different
concentrations.

30 In the first animal study in Example 1, the
degree of pain experienced by the mice after injection by
acetic acid is seen by the number of writhes. If the
mice experience no pain, there is no writhing. As would
be expected, if a pain reliever is not administered to

5 the mice prior to injection of acetic acid, the mice will exhibit writhing.

The protocol is based on the acetic acid writhing test in mice, developed by R. Koster, et al. Fed. Proc, 18, 412 (1939), and referred to a Koster test and Hunskaar, S., et al., J. Neuroscience Meth. 14: 69-76, 1985.

10

5

EXAMPLE 1

Test substance was administered PO (30 or 100 mg/kg) to groups of 3 ICR derived male or female mice weighing 22 ± 2 gms one hour before injection of acetic acid (0.5%, 20 ml/kg IP). Reduction in the number of writhes by 50 percent or more ($\geq 50\%$) per group of animals observed during the 5 to 10 minute period after acetic acid administration, relative to a vehicle treated control group, indicated analgesic activity.

The results are tabulated hereinbelow:

15

TABLE 1**Protocol #50390 Analgesia, Acetic Acid Writhing**

Compound	Route	Dose	No.	No.	% Inh. of Writhes
Distilled water	PO	20 ml/kg	1	17	0
Distilled water	PO	20 ml/kg	2	12	
Distilled water	PO	20 ml/kg	3	18	
Distilled water					
$\bar{X} \pm \text{SEM}$					15.7 \pm 1.9
Compound I	PO	100 mg/kg	1	0	100
Compound I	PO	100 mg/kg	2	0	
Compound I	PO	100 mg/kg	3	0	
$\bar{X} \pm \text{SEM}$					0 \pm 0
Compound I	PO	30 mg/kg	1	18	4
Compound I	PO	30 mg/kg	2	12	
Compound I	PO	30 mg/kg	3	15	
$\bar{X} \pm \text{SEM}$					15 \pm 1.7
Aspirin	PO	100 mg/kg	1	0	100
Aspirin	PO	100 mg/kg	2	0	
Aspirin	PO	100 mg/kg	3	0	
$\bar{X} \pm \text{SEM}$					0 \pm 0

Note: Compound I, at a dose of 100 mg/kg, 3 out of 3 animals showed slight convulsions 15 minutes after oral administration.

5 As clearly shown, the administration of
compound I at 100 mg/Kg was effective in reducing pain,
as indicated by the number of writhes. In fact, when
compound I was administered at 100 mg/Kg, the mice
experienced no writhes after acetic acid administration.
10 The same result was seen with aspirin, a known analgesic.

 This next experiment shows that the compounds
of the present invention are also effective in reducing
pain resulting from tissue injury, such as that caused by
15 injecting a small amount of formalin subcutaneously into
the hindpaw of a mouse.

5

EXAMPLE 2

Test substance was administered (30 or 100 mg/kg) to groups of 5 ICR derived male or female mice weighing 22 ± 2 gms one hour before subplantar injection of formalin (0.02 ml, 5%). Reduction of the induced hind paw licking time recorded during the following 20 to 30 minutes period by 50 percent or more ($\geq 50\%$) indicated analgesic activity.

The results are tabulated hereinbelow:

TABLE 2

	Compound	Route	Dose	N	Licking Time(sec.)		% Inh.
					Indiv.	Ave.	
	Distilled water	PO	20 ml/kg	1	146		
	Distilled water	PO	20 ml/kg	2	150		
	Distilled water	PO	20 ml/kg	3	121		
	Distilled water	PO	20 ml/kg	4	134		
	Distilled water	PO	20 ml/kg	5	88	128	0
	Compound I	PO	100 mg/kg	1	0		
	Compound I	PO	100 mg/kg	2	0		
	Compound I	PO	100 mg/kg	3	0		
	Compound I	PO	100 mg/kg	4	0		
	Compound I	PO	100 mg/kg	5	0	0	100
	Compound I	PO	30 mg/kg	1	122		
	Compound I	PO	30 mg/kg	2	125		
	Compound I	PO	30 mg/kg	3	62		
	Compound I	PO	30 mg/kg	4	127		
	Compound I	PO	30 mg/kg	5	63	100	22
	Aspirin	PO	300 mg/kg	1	30		
	Aspirin	PO	300 mg/kg	2	36		
	Aspirin	PO	300 mg/kg	3	51		
	Aspirin	PO	300 mg/kg	4	9		
	Aspirin	PO	300 mg/kg	5	54	36	72

Note: Compound I, at a dose of 100 mg/kg, 5 out of 5 animals showed slight convulsions at 15 minutes after oral administration.

5 The results clearly show that at 100 mg/Kg,
there was less licking by the mice than when aspirin was
administered at 300 mg/Kg. Therefore, this shows that
the compounds of the present invention are more effective
than aspirin in reducing pain from tissue damages.

10 The following example illustrates that the
compounds of the present invention are not antagonists of
the opioid receptor.

5

EXAMPLE 3

Groups of 4 male ICR mice weighing 22 ± 2 gms were employed. A dose (30 mg/kg) of test compound dissolved in a vehicle of saline was administered intraperitoneally. The control group received vehicle alone. At pretreatment (0 minute) a focused beam of radiant heat was applied to the middle dorsal surface of the tail to elicit a tail flick response within 6-7.5 seconds in pre-treated animals. A maximum cut-off time of 15 seconds was set. The time required to elicit a pain response was recorded for each animal at 0 and 30 minutes following administration of test compound. Prolongation by 50 percent or more ($\geq 50\%$) of the time required to elicit a tail flick indicated analgesic activity.

The results are as indicated hereinbelow:

TABLE 3

Compound	Route	Dose	N	Response Time		% Inh.
				0 Min.	30 Min.	
Saline (Vehicle)	IP	20 ml/kg	1	6.2	6.2	0
Saline (Vehicle)	IP	20 ml/kg	2	6.6	5.6	
Saline (Vehicle)	IP	20 ml/kg	3	7.0	5.3	
Saline (Vehicle)	IP	20 ml/kg	4	6.3	5.7	
\bar{x}				6.5	5.7	
SEM				0.2	0.2	
Compound I	IP	30 mg/kg	1	6.4	5.8	0
Compound I	IP	30 mg/kg	2	7.3	5.0	
Compound I	IP	30 mg/kg	3	6.4	6.0	
Compound I	IP	30 mg/kg	4	6.5	6.2	
\bar{x}				6.7	5.8	
SEM				0.2	0.3	
Morphine	IP	10 mg/kg	1	7.4	>15	100
Morphine	IP	10 mg/kg	2	6.5	>15	
Morphine	IP	10 mg/kg	3	6.4	>15	
Morphine	IP	10 mg/kg	4	7.4	>15	
\bar{x}				6.9	15.0	
SEM				0.3	0.0	

5 The data show that the radiant heat induced
tail flick response was unaffected by administration of
the compound at 30 mg/Kg. On the other hand, morphine
gave a positive response. This data show that Compound I
10 i.e., Compound I does not function through an opioid
receptor.

 The compounds of the present invention do not
have affinity for the serotonin 5-HT_{1A} receptor as
determined by a challenge with the 5 HT_{1A} agent, 5-
15 methoxy-N,N-dimethyltryptamine, as shown by the following
example.

5

EXAMPLE 4

Test substance was administered PO (30 mg/kg) to a group of 3 Long Evans derived male or female rats weighing 150 ± 20 gms one hour before injection of 5-MeODMT (5-methoxy-N,N-dimethyltryptamine, 3 mg/kg IP). Each animal exhibiting more than 2 head twitches during the ensuing 1 to 5 minute observation period was considered positive. Positive responses occurring in 2 or more (≥ 2) of the 3 animals was considered a significant effect

The results are tabulated hereinbelow:

TABLE 4

Compound Ave.	Route	Dose	No	Head Twitch	
Distilled water (Vehicle)	PO	10 ml/kg	1	0	
Distilled water (Vehicle)	PO	10 ml/kg	2	0	
Distilled water (Vehicle)	PO	10 ml/kg	3	0	0
Compound I	PO	30 mg/kg	1	2	
Compound I	PO	30 mg/kg	2	0	
Compound I	PO	30 mg/kg	3	0	1
Diazepam	PO	10 mg/kg	1	3	
Diazepam	PO	10 mg/kg	2	0	
Diazepam	PO	10 mg/kg	3	2	2

No potentiation of 5-MeODMT-induced heat twitch was observed utilizing 30 mg/Kg of the representative compound PO.

5

EXAMPLE 5

Test substance was administered ICVT (intracerebroventricular, 30 μ g in 5 μ l/mouse). The appearance of convulsions/mortality in 2 or more (≥ 2) of 3 ICR derived male or female mice weighing 22 \pm 2 gms within the 5 minutes thereafter would indicate NMDA receptor agonism. At a dose where no significant agonist activity was seen within 5 minutes, ability to inhibit NMDA (60 mg/kg IV)- induced Tonic convulsions/mortality in 2 or more (≥ 2) of 3 ICR derived male or female mice weighing 22 \pm gms within the following 5 minutes indicated NMDA receptor antagonist activity.

The results are tabulated hereinbelow:

20

TABLE 5

25

Compound Route Conc. N Agonism
Antagonism

30

Vehicle (Saline)	ICVT	5 μ l/mouse	3	0	0
Compound I	ICVT	30 μ g/mouse	3	0	1
Cis-4-Phosphono-methyl-2-piperidine-carboxylic acid*	ICVT	0.2 μ g/mouse	3	0	3
NMDA	ICVT	1 μ g/mouse	3	3	--

35

*a known potent antagonist at the glutamate site of the NMDA receptor

5 Note: Compound I, at a dose of 30 μ g/mouse, 2
out of 3 animals showed tremors without convulsions
after intracerebroventricular administration.

 The data indicate that the compounds did not
directly inhibit the effects of NMDA activity when 30
10 ug/mouse was administered intracerebrally.

 The results hereinabove in the writhing test
further demonstrate that the compounds of the present
invention have analgesic activity for the treatment of
pain, including inflammatory pain, e.g., rheumatoid
15 arthritis.

EXAMPLE 6**NMDA Induced Hyperalgesia**

Holtzman male rats weighing 275 to 325 grams were prepared with lumbar intrathecal catheters under isoflurane anesthesia. The catheters were externalized on the back of the head. Four to five days after implant, the animals were employed.

NMDA administration was accomplished using a gear driven microinjection syringe connected to the spinal catheter by a length of calibrated PE-90 tubing. The catheter plug was immediately replaced to avoid back flow and the rat was replaced in its testing box.

A modified Hargreaves box was used which allows the direction of a focused light beam on the underface of the paw through a glass surface upon which the rat stands. Surface temperature was maintained at 30°C. Withdrawal of the paw was taken as the response. Lack of response within twenty seconds was cause to terminate the test and assign that score.

The rats were placed on the thermal escape box and allowed to acclimate for 30 minutes prior to testing. A measurement was taken for each hindpaw to establish an average baseline latency (counted as time = 0). (2R)-2-(acetylamino)- N-[(4-fluorophenyl)methyl]-3-methoxypropanamide solution, that is, test product in this experiment, was given at an intrathecal dose of 1 µg/10 µl 10 minutes prior to intrathecal NMDA. A control group was given an identical amount of saline 10 minutes prior to intrathecal NMDA. Measurements were then made at 15, 30, 60, 120, 240 and 360 minutes after

5 intrathecal NMDA injection. General behavior
assessments were made during each period of observation
and include: tactile allodynia (vocalization/agitation
induced by light touch applied to the body surface),
spontaneous vocalization, biting and chewing of body
10 surface, loss of hind limb placing and stepping reflex,
loss of hind limb weight bearing and loss of righting
reflex.

The saline group (n=2) displayed a
hyperalgesic effect with a baseline latency of
15 approximately 1- second dropping to about 7 seconds
after about 45 minutes. The test product group (n=2)
maintained a normal baseline of about 14 second out to
20 minutes post NMDA injection and then dropping in
latency to approximately 10 seconds.

20 The preliminary data with the NMDA induced
thermal hyperalgesic suggest that the 2R-2-
(acetylamino)-N-[(4-fluorophenyl)methyl]-3-
methoxypropanamide had measurable anti-hyperalgesic
actions.

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EXAMPLE 7

Sprague Dawley male rats weighing 275 to 325 grams was used in this experiment. In this experiment, the response to neuropathic pain was determined. The neuropathic preparation used to induce an allodynic state is the surgical procedure described by Kim and Chung in Pain, 1992, 50,355-363 (1992) and outlined in Chaplain, et al. in J. Neurosci. Meth., 1994, 53, 355-363. Briefly, the left L₅ and L₆ spinal nerves were isolated adjacent to the vertebral column and ligated with 6-0 silk suture distal to the dorsal root ganglion under isoflurane anesthesia. The rats were allowed a minimum 7 day postoperative recovery period before placement in the study.

Testing groups consisted of 6 rats per group. Each group received test article, (2R)-2-acetyl-amino)-N-[(4-fluorophenyl)methyl]-3-methoxypropanamide (hereinafter "test article"), in one of three concentrations delivered intraperitoneally; the high concentration was 50 mg/kg, the medium concentration was 30 mg/kg and the low concentration was 20 mg/kg. One group of 6 rats received saline control solution at a volume equal to that used for test article.

General behavioral assessments were made during each period of observation and include: tactile allodynia (vocalization/agitation induced by light touch applied to the body surface), spontaneous vocalization, biting and chewing of body surface, loss of hind limb placing and stepping reflex, loss of hind limb weight bearing, and loss of righting reflex. All assessments

5 were noted as "present", "absent" or ranked according to a graded scale.

To assess tactile thresholds, rats were placed in a clear plastic, wire mesh-bottomed cage, divided into individual compartments. Animals were allowed to accommodate and then baseline thresholds were taken prior to drug treatment. To determine the 50% mechanical threshold for paw withdrawal, von Frey hairs were applied to the plantar mid-hindpaw, avoiding the tori (footpads). The eight von Frey hairs used are designated by $[\log (10 * \text{force required to bend hair, mg})]$ and range from 0.4-15.1 grams. Each hair was pressed perpendicularly against the paw with sufficient force to cause slight bending, and held for approximately 6-8 seconds. A positive response was noted if the paw was sharply withdrawn. Flinching immediately upon removal of the hair was also considered a positive response. Absence of a response ("-") was cause to present the next consecutive stronger stimulus; a positive response ("+") was caused to present the next weaker stimulus. Stimuli were presented successively until either six data points were collected, or the maximum or minimum stimulus was reached. If a minimum stimulus was reached and positive response still occurred, the threshold was assigned an arbitrary minimum value of 0.25 grams; if a maximum stimulus was presented and no response occurred, a maximum threshold value of 15 grams was assigned. If a change in response occurred, either "-" to "+" or "+" to "-", causing a change in the direction of stimulus presentation from

5 descending to ascending or vice-versa, four additional data points were collected subsequent to the change. The resulting pattern of responses were tabulated and the 50% response threshold computer using the formula:

10
$$\log (\text{threshold, mg} \times 10) = X_f + k_h$$

wherein:

X_f = value of the last von Frey hair applied;

k = correction factor based on response pattern (from calibration table)

15 h = mean distance in log units between stimuli.

Based on observations on normal, - operated rats and sham-operated rats, the cutoff of a 15.1-g hair is selected as the upper limit for testing.

20 The test was performed to establish an average baseline value, counted as time 0; then again at 15, 30, 60, 120 and 240 minutes after the dosing by the control saline solution or the test article.

The results were as follows:

25 Four rats were examined at intraperitoneal (IP) doses of 30 to 100 mg/kg.

One rat was given 100 mg/kg of the test article and within 15 minutes the rat was laterally recumbent displaying seizures and bleeding from the nose. The animal was euthanized.

30 A second rat was given 90 mg/kg of the test article and within 15 minutes the animal became catatonic and unable to right itself. The animal became

5 flaccid and displayed severe exophthalmos. Thirty minutes later there was no change and the animal was euthanized.

A third animal was given 60 mg/kg of the test article and within 15 minutes the animal became catatonic and displayed abnormal ambulation. Severe
10 exophthalmos was also noted. Thirty minutes later, the animal's ambulation appeared worse and it was subsequently euthanized.

A fourth rat was given 50 mg/kg of the test article. The rat appeared slightly catatonic which
15 lasted 60 minutes. No other behavioral deficits were noted.

A fifth rat was given 30 mg/kg of the test article IP and it displayed no behavioral deficit.

Fifteen mg/kg of the test article had
20 previously been shown to have no observable affect.

Using the Chung Model a dose dependent response was seen. The effect lasted approximately 2 hours after injection. Rats given the high dose of 50 mg/kg IP showed a threshold increase from 2 to 11 grams.
25 Behaviorally 6 of 6 rats appeared sedated for approximately 1 hour post injection. No other deficits were noted. Rats given 20 mg and 30 mg/kg test article showed an increase in threshold from approximately 2 to 5 grams. Four of 6 rats given 30 mg appeared sedated for
30 approximately 1 hour. No other deficits were noted. Previous study of 15 mg/kg showed no effect on the Chung Model. Group comparisons using one-way ANOVA performed on maximum effect, area under the curve and on specific time points (15 and 30 minutes post injection) showed no

5 significant difference between groups. The
nonparametric Jonckheere Test of ordered alternatives
was performed and showed a dose related difference at
the $p < 0.05$ level.

10 Test Article delivered intraperitoneally
resulted in a significant reversal of tactile allodynia
otherwise observed in the Chung model of neuropathy.
This model has historically been shown to be affected by
a number of clinically relevant agents, such as alpha 2
adrenergic agonists, NMDA receptor antagonists and N-
15 type Ca channel blockers. Importantly, these
observations occurred at doses that were believed to be
without significant effects upon competing behaviors
(e.g., sedation or motor impairment).

20 The above preferred embodiments and examples
are given to illustrate the scope and spirit of the
present invention. The embodiments and examples
described herein will make apparent to those skilled in
the art other embodiments and examples. These other
embodiments and examples are within the contemplation of
25 the present invention. Therefore, the present invention
should be limited only by the appended claims.